ISSN 2782-1730

hospital

Medical Bulletin of the Main Military Clinical Hospital named after N.N. Burdenko

hospitalburdenko.com

21
Application of activated conditioned plasma in patients with macular rupture

38
Non transfusion dependent thalassaemia: conventional and novel therapy

2022 №2

2022 №2

ISSN: 2782-1730 (PRINT) / ISSN: 2713-0711 (ONLINE)
DOI: 10.53652/2782-1730-2022-3-2

PEER-REVIEWED
SCIENTIFIC AND PRACTICAL JOURNAL
MEDICAL BULLETIN OF THE MAIN MILITARY
CLINICAL HOSPITAL
NAMED AFTER N.N. BURDENKO

The journal's articles are included in the independent database of the complete list of scientific papers — the Russian Science Citation Index (RSCI).
Free access policy.
Electronic versions of the published issues of the journal are available online: hospitalburdenko.com

MEDICAL BULLETIN OF THE MAIN MILITARY CLINICAL HOSPITAL NAMED AFTER N.N. BURDENKO

Production: Publishing House Opinion Leader by order of Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry
Phone: +7 926 317 4445

2022 №2

CONTENTS

4
ORIGINAL RESEARCH
UDK 616-007.17
DOI: 10.53652/2782-1730-2022-3-2-05-11
Fibromuscular dysplasia: a review of the literature and case reports
Fursov A.N., Potekhin N.P., Lyapkova N.B., Gorodnichev K.Y.

10
ORIGINAL RESEARCH
UDK 611.423
DOI: 10.53652/2782-1730-2022-3-2-12-17
Comparison of efficiency of methylene blue preparations for visualization of lymph drainage pathways in the experiment
Kovalenko V.V., Barinov O.V., Fufaev E.E., Dmitrochenko I.V., Kurakevich I.V.

15
ORIGINAL RESEARCH
UDK 616-006.699
DOI: 10.53652/2782-1730-2022-3-2-18-24
Treatment of non-small cell lung cancer using radiation therapy
Gevorkian A.R., Smolin A.V.

21
ORIGINAL RESEARCH
UDK 611.018.54
DOI: 10.53652/2782-1730-2022-3-2-26-34
Application of activated conditioned plasma in patients with macular rupture
Pavlov V.A., Kurnosov V.E., Zinovyev S.A., Kapatsina A.A., Utkina E.E.

28
ORIGINAL RESEARCH
UDK 581.143.4
DOI: 10.53652/2782-1730-2022-3-2-36-43
Hemodynamic monitoring in liver transplantation
Zhuravel S.V., Kuznetsova N.K., Statsura V.E., Gavrilov P.V., Goncharova I.I.

34
CLINICAL OBSERVATION
UDK 616.152.112
DOI: 10.53652/2782-1730-2022-3-2-44-47
Extracorporeal detoxification in intensive care of metabolic acidosis in cancer patients
Gromova E.G.

38
LECTURE
UDK 616.155.194.125
DOI: 10.53652/2782-1730-2022-3-2-48-59
Non transfusion dependent thalassaemia: conventional and novel therapy
Asadov Ch.D.

48
LECTURE
UDK 616-079.4
DOI: 10.53652/2782-1730-2022-3-2-60-77
Differential diagnosis of essential arterial hypertension and neurocirculatory asthenia of the hypertensive type
Datsko A.V., Orlov F.A., Petrova O.N., Emanova I.A.

Fibromuscular dysplasia: a review of the literature and case reports

UDK 616-007.17
DOI: 10.53652/2782-1730-2022-3-2-5-11

Fursov A.N., Potekhin N.P., Lyapkova N.B., Gorodnichev K.Y.

Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia

Abstract. This article provides information on the prevalence of fibromuscular dysplasia and its role in the development of arterial hypertension, as well as gives the classification, summarizes approaches to diagnosis and treatment, describes cases of different localization of fibromuscular dysplasia and individual (personalized) management tactics for this category of patients.

Keywords: fibromuscular dysplasia, arterial hypertension, vasorenal hypertension, treatment of fibromuscular dysplasia.

Introduction. Fibromuscular dysplasia (FMD) is a rather rare idiopathic, segmental cardiovascular disease of non-atherosclerotic and non-inflammatory origin, with lesions of medium- and small-diameter muscular arteries, leading to their stenosis [1]. According to literature data, the prevalence of FMD in the population is 4 cases per 1000 people. The disease is most frequently diagnosed in women aged 15-50 years [2, 3]. Typical localization of FMD is renal (74.3%) and/or carotid (79.7%) arteries, lesions of vertebral, visceral (mesenteric), iliac and coronary arteries occur much less frequently [1, 4, 5]. According to the 2014 European consensus, FMD is diagnosed in more than one vascular pool in 66.3% of cases [1, 5].

The etiology of FMD is not exactly understood. The main role in the development of the disease is attributed to genetic factors. In some cases, there is an autosomal dominant type of inheritance; FMD is often associated with Ehlers-Danlos, Marfan, and Alport syndromes [3]. In addition, there are assumptions about the influence of environmental factors (trauma, smoking), mechanical vascular stress during life, the level of female sex hormones on the development of the disease [4, 6, 7].

The first description of FMD dates back to 1938, when W. Leadbetter and L. Burkland pioneered to describe the clinical manifestations of severe arterial hypertension (AH) in a 5-year-old African-American boy with an altered renal artery due to its narrowing caused by a hypertrophic muscular layer [4]. Subsequently, in 1958, L.J. McCormack et al. described 4 cases of vasorenal AH in patients with fibromuscular hyperplasia of the renal arteries. In 1965, L. Hunt et al. introduced the term "fibromuscular dysplasia", indicating the morphological heterogeneity of this disease, manifested not only by hyperplasia [8]. In 1971, a histological classification of renal artery lesions was published, including lesions of different layers of the vessel wall: intima, medium or adventitia [4, 8]. In this connection, FMD can be one of the reasons not only for the development of stenoses of the above mentioned arteries, but also for their aneurysms and dissections [1].

Diagnostics. It should be noted that the diagnosis of the disease is primarily based on imaging techniques rather than histological findings, which are not always available in clinical practice.

The clinical picture of FMD is nonspecific and can vary from asymptomatic course (then it becomes a finding during the investigations), to acute coronary syndrome with the development of coronary artery dissection against its background [9, 10]. Taking into account the absence of specific signs of FMD, it should be assumed in the presence of resistant AH in young and middle-aged women without cardiovascular risk factors. In addition, FMD should be excluded in middle-aged individuals with neurological symptoms such as headache, pulsating or non-pulsating tinnitus, dizziness, neck pain, which may indicate the development of aneurysm, carotid or vertebral artery dissection against the background of this pathology.

In the therapeutic community the term FMD is associated with vasorenal hypertension, although stenotic hemodynamic disorders of any vascular pool, in particular brachiocephalic arteries, in the program of compensatory (adaptive) blood pressure (BP) increase may also be at the origin of the symptomatic (secondary) nature of AH.

Currently, based on the results of angiography ("gold standard" in the diagnosis of FMD), a classification is proposed, including a multifocal lesion with alternating areas of stenosis and dilatation ("string of beads") (type I), detected in the middle and distal part of the vessel, a focal (local, <1 cm) artery lesion (type II) occurring in any part of the vessel, tubular (≥1 cm) lesion with thickening of the walls along the vessel (type III).

A comparison of angiographic and histological examination results showed that multifocal lesions were associated with fibrodysplasia of the media (in 70% of cases), local — with fibrodysplasia of the intima (in 5% of cases), tubular — with fibrodysplasia of the adventitia (in 15-25% of cases) [11].

These three types are not mutually exclusive. There are observations about the presence of medial and perimedial types of FMD in the same segment, in others — the lesion of several arteries, often of different types [8].

A characteristic feature of FMD according to angiography is its localization in the middle and distal segments of the artery (in particular, the renal artery) in contrast to atherosclerotic lesion, in which its proximal segment is more often involved or there is orifice stenosis [12]. In more than a quarter of cases (27%) the other variant of FMD development is aneurysms [13].

Multispiral computed tomographic angiography is currently as sensitive (88-100%) and specific (up to 99%) as X-ray contrast angiography, as well as less invasive [5, 14]. It should be noted that a number of publications point out its low informativity in the diagnosis of stenoses of small branches of the renal artery [3, 15].

Ultrasound methods of arterial bed imaging allow the diagnosis of renal and carotid artery stenoses, but it is impossible to distinguish the atherosclerotic or stenotic genesis of these lesions in FMD. In this case, ultrasound diagnostic methods are inferior to contrast angiography in the presence of aneurysmal changes of the vascular wall in the absence of significant stenoses. Furthermore, imaging quality decreases in case of obesity, intestinal pneumatosis, and a number of other conditions [3].

Laboratory methods of FMD diagnosis, in particular the examination of blood plasma renin level in vasorenal AH, cannot specify the etiology of hypertension.

Treatment. Treatment approaches in FMD are based on expert opinion — due to the lack of multicenter randomized trials, which determines the difficulty in choosing a treatment tactic. A conventional and surgical approaches are distinguished.

Conventional treatment consists of non-medication interventions to eliminate the well-known risk factors for cardiovascular diseases (tobacco smoking, hypodynamia, excessive weight, etc.), as well as the prescription of drug therapy. Considering that the most frequent clinical manifestation in FMD is a syndrome of resistant (refractory) AH, antihypertensive drugs (AHD) are used, generally in various combinations. The prescription of statins and antiaggregants is strictly individualized, with regard to the risk of cardiovascular complications according to the SCORE scale, when its values are more than 5% [1, 4, 5].

Endovascular techniques are used for stenosis over 60%, accompanied by refractory to drug therapy AH, and if there is a history of left ventricular insufficiency (pulmonary edema). Additionally, such interventions can be organ-preserving [1, 3, 4, 5].

At present, endovascular methods should be considered as the therapy of choice along with medication component for FMD treatment. Presence of renal size asymmetry more than 1.5 cm and stage 3 chronic kidney disease result in low efficiency of BP normalization and worsen the prognosis [16]. It should be kept in mind that despite the technical success of renal revascularization, in both open and endovascular methods of FMD correction, almost half of patients require continuation of AHD [17].

For aneurysmal type of FMD, the prevailing opinion is that aneurysms less than 1 cm ("string of beads") have a favorable course after stenosis elimination. Concerning the treatment of aneurysms 1-2 cm in size, the conventional approach to the management of patients prevails, with the focus on achieving target BP levels, which improves their prognosis. Aneurysms larger than 2 cm are considered for surgical treatment [18]. Combined lesion of arterial bed with both stenotic lesion and pathological

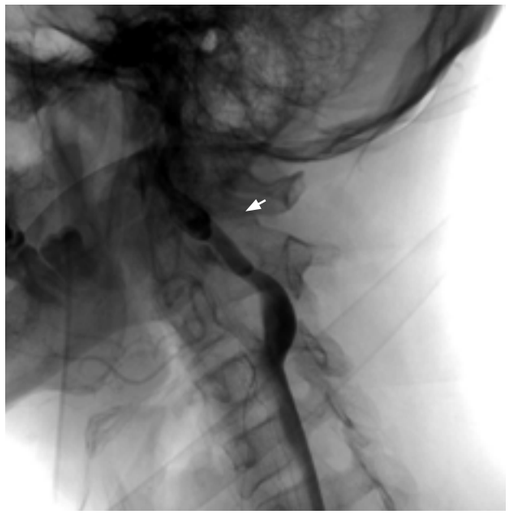


Fig. 1. Fibromuscular dysplasia of the left internal carotid artery with aneurysm (shown by arrow)

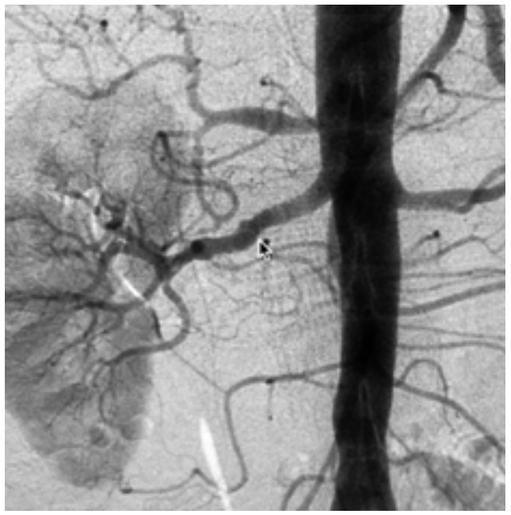


Fig. 2. Fibromuscular dysplasia of the right renal artery (shown by arrow)

tortuosity, with formation of multiple aneurysms, requires reconstructive interventions [1, 3, 5, 8].

Considering the difficulties in the choice of management tactics of patients with FMD, here are several clinical cases.

Clinical case No. 1. Resistant, secondary AH due to carotid and renal artery FMD: successful open surgical treatment of a patient with carotid artery FMD and formation of an aneurysm in its background.

Patient G., 43 years old, was admitted to The Main Military Clinical Hospital named after N.N. Burdenko with complaints of recurrent headaches and dizziness. The patient It was known from the medical history that he had been diagnosed with AH for more than 15 years, in the last years his hypertension was refractory: grade 2-3 AH, with a pronounced diastolic component against the background of 5-component antihypertensive therapy (AHT), including diuretic.

During the examination of the patient according to ultrasound duplex scanning (USDS) of the renal and carotid arteries no significant pathology was detected, no data on systemic arterial lesions (vasculitis) were obtained, lipid metabolism was not impaired. Considering the resistant character of AH with a pronounced diastolic component, it was decided to perform contrast angiography. According to aortography: signs of left internal carotid artery (ICA) type I ("string of beads"), aneurysm of the I segment of the left ICA, in the distal part of the right renal artery contour irregularity with moderately dilated area (signs of FMD of the right renal artery) (Fig. 1 and 2).

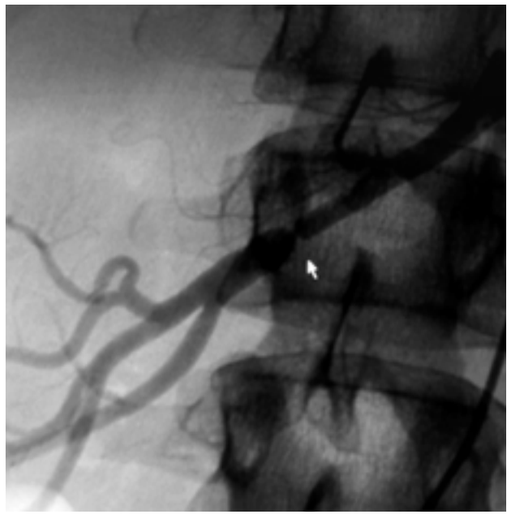
Considering the nature and localization of FMD, a consilium of leading hospital specialists decided on surgical treatment of FMD of the left ICA. As for right renal artery FMD, with regard to the absence of hemodynamically significant narrowing, it was decided to choose conventional management tactics. The consilium considered that AH in this clinical situation was of secondary (compensatory) nature due to combined intrarenal and cerebral hemodynamic disturbances.

The patient underwent carotid endarterectomy from the main carotid artery on the left side, resection of ICA aneurysm, prosthetics of the left ICA with a synthetic 6 mm polytetrafluoroethylene (PTFE) prosthesis.

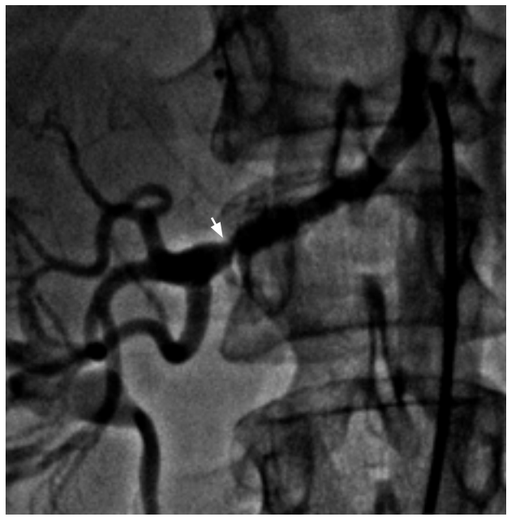
The postoperative period proceeded without any peculiarities. Immediately after the surgical intervention, there was a decrease of BP to the 1st degree of AH (BP 150/90 mm Hg), which required significant de-escalation of AHT. At the time of discharge from the hospital, BP was maintained at the target values by three AHTs in subtherapeutic doses (valsartan 80 mg/day, amlodipine 5 mg/day, metoprolol 50 mg/day).

Clinical case No. 2. Resistant, secondary AH due to the right renal artery FMD: angioplasty with FMD stenting in 2015, restenosis distal to the stent — recurrent angioplasty with stenting of the right renal artery in 2019.

Patient G., 37 years old, was admitted to the hospital for diagnosis clarification due to resistant AH of the 3rd grade (BP increase up to 240/140 mm Hg) against the background of 4-component AHT, which included angiotensin II receptor blocker, dihydropyridine-type calcium



A



B

Fig. 3. A — Major stenosis of the right renal artery against the background of type III fibromuscular dysplasia (shown by arrow); B — restenosis of the right renal artery up to 80% at the distal edge of the stent (shown by arrow)

Considering the difficulties in the choice of management tactics of patients with fibromuscular dysplasia, here are several clinical cases

channel blocker, central imidazoline receptor agonist and diuretic. The duration of AH was 2 years.

The examination revealed hemodynamically significant stenosis of the right renal artery. According to angiography on May 23, 2015: renal arteries branch off by one to each kidney. Intrarenal pattern and the kidneys themselves are of normal size, without features. The right renal artery in the middle third approximately 3 cm along is irregularly narrowed from 50 to 96% (within FMD). The left renal artery has smooth contours and a uniform lumen (Fig. 3A).

On May 30, 2015 the patient underwent balloon angioplasty with endoprosthesis of the right renal artery (5.5-12 Herculink stent). The postoperative period proceeded in a standard manner. In the early postoperative period, BP values stabilized at 120-130/80-90 mm Hg. The patient was recommended to receive dual antiaggregant therapy for 3-6 months, as well as bisoprololol 5 mg/day.

Until November 2019, the patient's condition remained stable, BP 130/80 mm Hg. Subsequently, there was a rise in BP to 2-3 Grade AH.

The control angiography of the renal arteries dated December 18, 2019 showed stenosis of the right renal artery of up to 80% in the area of the distal edge of the stent (Fig. 3B).

No information about atherosclerosis and lipid metabolism abnormalities was obtained during the examination. It was decided to perform angioplasty and stenting of the right renal artery. Postoperative period was standard, BP values stabilized at 120/80 mm Hg immediately after the intervention. The patient was discharged in satisfactory condition under the supervision of the outpatient clinic specialists and was recommend-

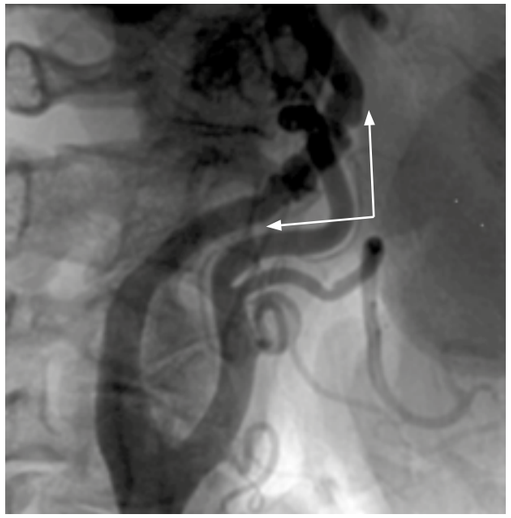


Fig. 4. Fibromuscular dysplasia of the right internal carotid artery (shown by arrow)

ed to receive dual antiaggregant therapy for 3-6 months.

Clinical case No. 3. Right carotid artery FMD.

Patient E., 48 years old, was admitted to the hospital due to detection of pathological tortuosity of the right carotid artery against the background of the existing "controlled" AH during ultrasound examination. It was decided to perform contrast angiography of the brachiocephalic arteries.

According to the aortography results dated March 15, 2019: the brachiocephalic trunk is markedly calcified proximally and in the bifurcation zone, the right common carotid artery is freely passable, the ICA is deformed in the middle third in the "string of beads" type with dilation up to 1-1.5 cm, the left one is without any peculiarities (Fig. 4).

Considering the nature and localization of FMD, hemodynamically insignificant carotid lesion, the consilium of leading hospital specialists decided on conservative treatment with ACE inhibitors and calcium channel antagonists to achieve target BP levels (130/80 mm Hg), statins under control of lipidogram values and antiaggregants.

Conclusion. Thus, the presented clinical cases revealed peculiarities in the diagnosis of FMD. Contrast angiography has been shown to be the "gold standard" in the diagnosis of FMD. In our opinion, angiography is reasonable for clinical suspicion of FMD in patients with resistant AH even with negative results of previous ultrasound imaging of the vessel.

In addition, the variety of therapeutic approaches to the management of this category of patients was demonstrated. In one case reconstructive intervention on the vessel was required, allowing not only to prevent aneurysm rupture, but also to make the course of AH "manageable". In the second case, endovascular elimination of significant renal artery stenosis allowed to normalize BP values, however, it should be noted that extended stenosis implicates the possibility of disease recurrence. In the third case, considering the angiographic picture of the artery lesion, it is acceptable to use only a conventional tactics of patient management.

The presented clinical cases revealed peculiarities in the diagnosis of FMD. Contrast angiography has been shown to be the "gold standard" in the diagnosis of FMD. In our opinion, angiography is reasonable for clinical suspicion of FMD in patients with resistant AH even with negative results of previous ultrasound imaging of the vessel

References

1. Persu A, Giavarini A, Touzé E, Januszewicz A, Sapoval M, Azizi M, et al. European consensus on the diagnosis and management of fibromuscular dysplasia. *J Hypertens.* 2014; 32(7):1367–78. https://doi.org/10.1097/HJH.0000000000000213
2. Plouin PF, Perdu J, La Batide-Alanore A, Boutouyrie P, Gimenez–Roqueplo AP, Jeunemaitreet X. Fibromuscular dysplasia. *Orph J Rare Dis.* 2007; 2:28. https://doi.org/10.1186/1750-1172-2-28
3. Arakelyan VS, Gidaspov NA, Kulichkov PP, Dorofeev AV, Getsadze GG. Fibromuscular dysplasia with the formation of multiple aneurysms and stenosis of the left renal artery. *Clinical physiology of circulation.* 2018; 15(3):215–221. (In Russ). https://doi.org/10.24022/1814-6910-2018-15-3-215-221

4. Trisvetova EL. Modern concepts of fibromuscular dysplasia of the coronary arteries. *Rational Pharmacotherapy in Cardiology.* 2019; 15(3):431–438. (In Russ). https://doi.org/10.20996/1819-6446-2019-15-3-431-438
5. Gornik HL, Persu A, Adlam D, Aparicio LS, Azizi M, Boulanger M, et al. First International Consensus on the diagnosis and management of fibromuscular dysplasia. *Vasc Med.* 2019; 24(2):164–189. https://doi.org/10.1177/1358863X18821816
6. Chernavskiy SV, Davydov DV, Stremoukhov AA, Kudentsova LA. *V pomoshch patsientu s sakharnym diabetom (sovety vracha)*. Moscow: GVKG im. N.N. Burdenko; 2021, 32 p. (In Russ).
7. Sergoventsev AA, Borisov IA, Dalinin VV, Steklov VI, Dieva TV. Heart surgery in the P.V. Mandryka central clinical hospital: establishment, present and future. *Military medical journal.* 2019; 340(5):16–20 (In Russ).
8. Cherednychenko YuV, Miroshnychenko AYu, Dziak LA, Zorin NA, Cherednychenko NA. Choice of treatment tactics of fibromuscular dysplasia of cerebral arteries. *Endovascularnaya neyrorentgenokhirurgiya.* 2015; 1(11):54–70 (In Russ).
9. Mogler C, Springer W, Gorenflo M. Fibromuscular dysplasia of the coronary arteries: a rare cause of death in infants and young children. *Cardiol Young.* 2016; 26(1):202–5. https://doi.org/10.1017/S104795111500061X
10. Fursov AN, Gaidukov AV, Chernov SA. Dissection of the coronary artery after exercise. *Clinical medicine.* 2021; 3(99):213–216 (In Russ).
11. Shivapour DM, Erwin P, Kim ESH. Epidemiology of fibromuscular dysplasia: A review of the literature. *Vasc Med.* 2016; 21(4):376–81. https://doi.org/10.1177/1358863X16637913
12. Bokhari MR, Bokhari SRA. *Renal Artery Stenosis.* Treasure Island (FL): StatPearls Publishing; 2017 [Internet. Available from: https://www.amboss.com/us/knowledge/Renal_artery_srenosis
13. Olin JW, Froehlich J, Gu X, Bacharach JM, Eagle K, Gray BH, et al. The United States Registry for Fibromuscular Dysplasia: results in the first 447 patients. *Circulation.* 2012; 125(25):3182–90. https://doi.org/10.1161/circulationaha.112.091223
14. Gasymov EG, Abdulgasanov RA. Fibromuscular dysplasia of renal arteries (modern methods of diagnosis and treatment. *Creative Cardiology.* 2018; 12(1):62–9 (In Russ). https://doi.org/10.24022/1997-3187-2018-12-1-62-69
15. Sabharwal R, Vladica P, Coleman P. Multidetector spiral CT renal angiography in the diagnosis of renal artery fibromuscular dysplasia. *Eur J Rad.* 2007; 61(3):520–7. https://doi.org/10.1016/j.ejrad.2006.10.005
16. Bumpus SM, Kuck C, Heidt ST. Diagnosed and living with fibromuscular dysplasia: A qualitative Inquiry. *Vasc Med.* 2016; 21:539–546. https://doi.org/10.1177/1358863X16668419
17. Weinberg I, Gu X, Giri J, Kim SE, Bacharach MJ, Gray BH, et al. Anti-platelet and anti-hypertension medication use in patients with fibromuscular dysplasia: results from the United States Registry for fibromuscular dysplasia. *Vasc Med.* 2015; 20(5):447–53. https://doi.org/10.1177/1358863X15584982
18. Gottsater A, Lindblad B. Optimal management of renal artery fibromuscular dysplasia. *Ther Clin Risk Manag.* 2014; 10:583–95. https://doi.org/10.2147/tcrm.s48746

Information about the authors:

Andrej N. Fursov — MD, DSc, Professor, Head of the Cardiology Department, Cardiology Centre of Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Nikolaj P. Potekhin — MD, DSc, Professor, deputy chief of Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Natal'ya B. Lyapkova — MD, PhD, cardiologist, Cardiology Department, Cardiology Centre of Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia — **responsible for contacts, bestuzhevaol@mail.ru**, ORCID: 0000-0003-4496-8884

Konstanin Yu. Gorodnichev — X-ray endovascular surgeon of the Department of X-ray Surgical Diagnostics and Treatment, Center of Cardiovascular Surgery, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

The authors declare no conflicts of interest.
The study was not sponsored.
Received 11.11.2021

Comparison of efficiency of methylene blue preparations for visualization of lymph drainage pathways in the experiment

UDK 611.423
DOI: 10.53652/2782-1730-2022-3-2-12-17

Kovalenko V.V.[1], Barinov O.V.[1], Fufaev E.E.[1], DmitrochenkoI.V.[1], Kurakevich I.V.[2]

[1] Military Medical Academy named after S.M. Kirov, Russian Defense Ministry, Saint-Petersburg, Russia
[2] Branch No. 1 of the Federal State-owned institution "439th Military Hospital" of the Ministry of Defense of the Russian Federation, Sergeyevka village, Border District, Primorsky Krai, Russia

Abstract. ***Objective.*** To compare and evaluate the effectiveness of using methylene blue solutions to visualize lymph drainage pathways in laboratory animals (outbred rat).

Materials and methods. In the experiment, 16 female outbred rats aged about 40 days, with an initial body weight of 180-220 g, kept in standard vivarium conditions, were used. Zolazepam (Zoletil®100) was used for anesthesia. Animals were randomized into 2 groups –~~8~~ in each. The first group was injected subcutaneously in the left thigh with a 1% aqueous solution of methylene blue, the second group –~~s~~olution of methylene blue with human serum albumin. Depending on the time of exposure, animals were divided randomly into 4 subgroups –~~1~~5, 30, 45 and 60 minutes. There was evaluated the effectiveness of marking the lymph drainage pathways from the injection site.

Results. The study demonstrated that the use of a 1% aqueous solution of methylene blue solution allows visualizing of the lymph drainage pathways when the preparation is exposed for 30 minutes. Staining of the lymph nodes of the next order occurs with an increase in exposure time. A solution of methylene blue in combination with human serum albumin stains the first node in the lymph drainage path 30 minutes after administration. The preparation is characterized by slow migration from the first-order lymph nodes (>60 minutes).

Conclusion. The use of methylene blue solution in combination with serum albumin is characterized by slow migration from the first-order lymph nodes, which makes its use preferable for surgical interventions.

Keywords: signal lymph node, non-small cell lung cancer, micrometastasis, N-staging, sentinel lymph node, methylene blue, human serum albumin.

Introduction. For the last years lung cancer occupies the leading position in the structure of oncological morbidity and mortality. More than 2 million new cases of lung malignancies are diagnosed annually in the world, 85-90% of which are represented by non-small cell lung cancer (NSCLC) [1]. Besides, more than 1 million 700 thousand people die annually due to the progression of cancer process. Despite the rapid development of medicine and oncology in particular, the long-term survival rate among men and women according to different sources remains around 19% [2]. Adequate treatment of early stage NSCLC (I-II) allows increasing the proportion of patients surviving the 5-year mark to 64% or more [3].

Preoperative detection of metastases in regional lymph nodes (LNs) is the most essential diagnostic step to determine the prognosis and tactics for further treatment [4]. In 20-30% of patients treated for stage I-II NSCLC, there is a local or distant reoccurrence of the disease, and 5-year survival rate in these patients varies from 40 to 85.5% [7]. One of the reasons for unsatisfactory results is the spread of tumor cells to regional nodes in the form of micrometastases, which are not detected by radiological diagnostics and routine histological examination [3].

Active use of low-dose computed tomography as a method of lung cancer screening has increased the proportion of patients with suspected lung malignancy [6, 8]. In stage I-II NSCLC, active surgical tactics should be used to diagnose and treat the pathological process [6]. The standard volume of intervention is lobectomy. However, recently, organ-preserving anatomical resections (segmentectomies) have been proposed. This volume of intervention can be performed only in the proven absence of lesions of regional LNs, which should be confirmed intraoperatively when determining the individual lymph drainage pathways.

Considering the above, there are prerequisites for the search of new methods that will improve the results of LN lesion diagnostics in patients with NSCLC. One of such techniques is intraoperative identification of the signal lymph node (SLN), as well as determination of individual type of lymph outflow. This approach makes it possible to identify the first lymph node on the path of lymphogenic spread of the cancer process and perform its targeted biopsy to determine the state of other regional LNs [5, 11].

However, to date, there is no "ideal" method for detecting SLN. The use of biological dyes, radioisotope preparations, fluorescent and radio-contrast substances has been suggested, yet each of these methods has disadvantages when applied in clinical practice, which makes the problem of finding an optimal method of intraoperative labeling of lymph drainage routes relevant [9, 10, 12, 13].

Purpose. To compare the efficiency of using 1% aqueous methylene blue (MB) solution and 1% aqueous methylene blue solution with human serum albumin (MB:HSA) in the experiment.

Materials and methods. The study assessed and compared the effectiveness of using blue aniline dyes for marking lymphatic outflow pathways in laboratory animals (mongrel rats). Sixteen female mongrel rats aged about 40 days with an initial body weight of 180-220 g kept in standard vivarium conditions (FSUE “Nursery of laboratory animals “Rappolovo”", Leningrad Region, Russia) were used in the experiment. Zolazepam (Zoletil®100) was used for anesthesia. All experimental work was carried out in accordance with the requirements of the international convention. Permission of the ethical committee of The S. M. Kirov Military Medical Academy was obtained.

The animals were randomized into two groups of 8 individuals each. The first group was injected 1% aqueous MB solution to mark the lymphatic outflow pathways, the second group — a mixture of 1% aqueous MB solution with 20% human serum albumin solution (MB:HSA). The preparations were injected using the same technique: after preliminary anesthesia, the marking solution was injected subcutaneously into the femoral segment of the left hind limb. After the injection, circular massaging movements were performed for 15 seconds at the injection site. Then, the animals were randomly divided into 4 subgroups depending on the exposure time of the solutions: 15, 30, 45, and 60 minutes.

After the time expired, the animals were removed from the experiment. An autopsy was performed to determine the efficiency of LN marking. Lymph nodes were verified based on the scheme presented in the literature. SLN biopsy with subsequent histological examination was performed. The purpose of the histological examination was to investigate the microscopic changes observed in the marked LN.

The use of methylene blue solution in combination with serum albumin is characterized by slow migration from the first-order lymph nodes, which makes its use preferable for surgical interventions

Table 1. Results of signal lymph node detection in rats

Group	15 minutes	30 minutes	45 minutes	60 minutes
1 Group (methylene blue)	–	+	++	–
2 Group (methylene blue + albumin)	–	+	+	+

Note: "-" — stained nodes are absent; "+" — a single stained node; "++" — several stained nodes.

Results. In all laboratory animals the effectiveness of intraoperative visualization of the lymphatic outflow pathways of the injection site of chromolymphotropic preparations (MB; MB:HSA) was evaluated. The effectiveness of the injected preparation for staining the lymphatic outflow pathways was determined based on the results of the visual evaluation (Table 1).

No differences were found in the groups (MB and MB + albumin) when the preparations were exposed for 15 minutes. This is probably due to insufficient time for the migration of the preparation from the point of injection (Fig. 1, 2).

Further, the results of SLN marking during exposure for 30 minutes were investigated. In the MB and MB:HSA groups, all 4 animals showed a single stained SLN, which was recognized as signaling (Figs. 3, 4).

When exposed for 45 minutes, 2 to 3 marked LNs of different order were detected in the MB group animals,

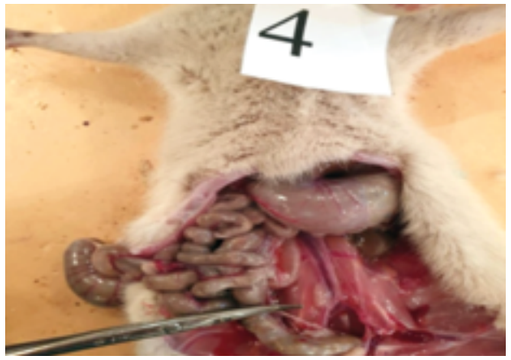


Fig. 1. Intraoperative photo: animal from MB group. SLN was not visualized

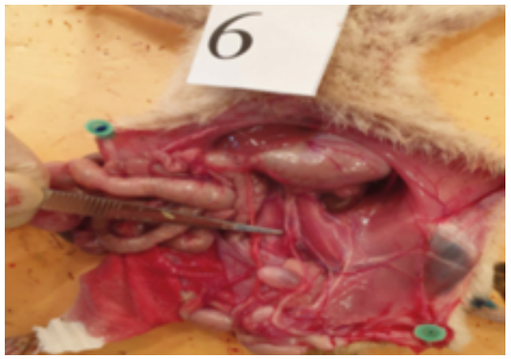


Fig. 2. Intraoperative photo: animal from MB:HSA group. SLN was not visualized

Fig. 3. Intraoperative photo: MB group animal. 1 SLN is visualized

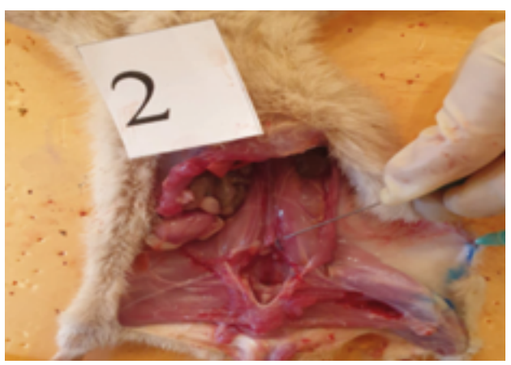


Fig. 4. Intraoperative photo: animal from the MB:HSA group. 1 SLN is visualized

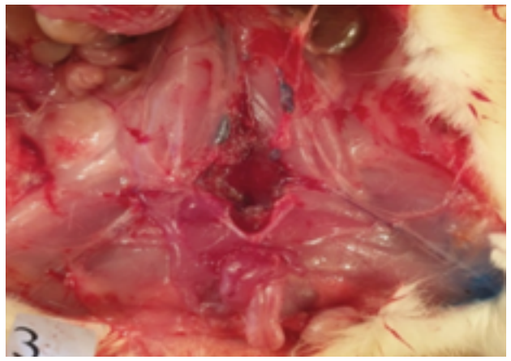


Fig. 5. Intraoperative photo: animal from the MB group. 3 SLNs of different orders are visualized

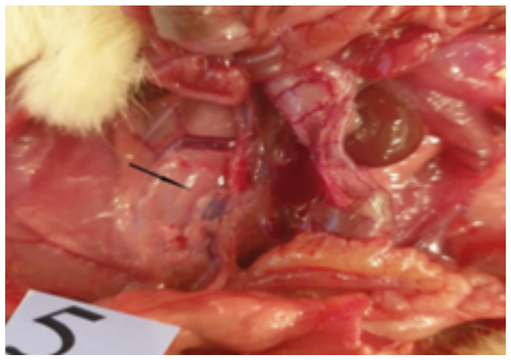


Fig. 6. Intraoperative photo: animal from MB:HSA group. 1 SLN is visualized

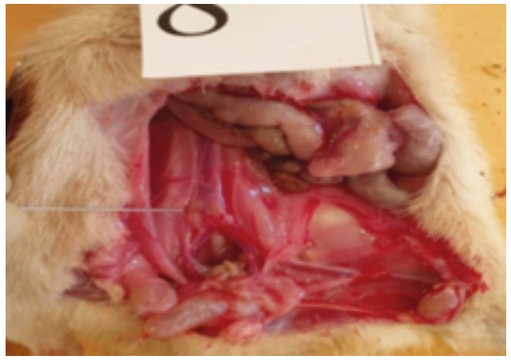


Fig. 7. Intraoperative photo: animal from the MB group. SLN was not visualized

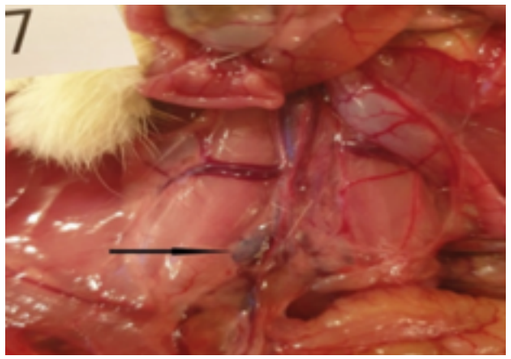


Fig. 8. Intraoperative photo: animal from MB:HSA group. 1 SLN is visualized

which is probably due to the migration of the preparation to the following collectors along the lymphatic outflow pathway. In the second group, both animals showed a single stained node in the iliac region. It is assumed that these differences are related to the molecular weight of the compounds and size, which makes the migration of MB:HSA longer through the first node in the lymphatic outflow pathway (Fig. 5, 6).

When exposed for 60 minutes, the results in the MB:HSA group were similar to the previous ones, however, the node staining was slightly less intense than after 30 and 45 minutes. In contrast, in the group in which MB was injected, no stained nodes were detected after 60 minutes (Figs. 7, 8).

Micro-preparations were made of the obtained marked LNs. The structure of LN remained unchanged, and no histological signs of MD staining were detected.

Thus, marking LN with blue dyes does not change the microstructure of the preparation, which is an important criterion in the search of micrometastases in LN.

Conclusions. 1. The use of 1% MB solution allows to adequately visualize the lymphatic outflow pathways. The disadvantage of the preparation is the migration to the next-order LN when exposed for 30 minutes.

2. MB solution in combination with human serum albumin has a comparable quality of LN visualization, although it has a delayed (>60 min) migration, which is preferable during surgery.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* 2019; 69(1):7–34.https://doi.org/10.3322/caac.21551

2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and

mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018; 68(6):394–424. https://doi.org/10.3322/caac.21492

3. Bille A, Woo KM, Ahmad U, Rizk NP, Jones DR. Incidence of occult pN2 disease following resection and mediastinal lymph node dissection in clinical stage I lung cancer patients. *Eur J Cardiothorac Surg*. 2017; 51(4):674–679. https://doi.org/10.1093/ejcts/ezw400
4. Akopov AL, Papayan GV, Chistyakov IV, Karlson A, Gerasin AV, Agishev AS. Intraoperative detection of sentinel lymph nodes using infrared imaging system in local non-small cell cancinoma of lung. *Grekov's Bulletin of Surgery*. 2015; 174(4):13–17. (In Russ.)]. https://www.elibrary.ru/item.asp?id=23904990
5. Amiraliev AM, Pikin OV, Ryabov AB, Bagrov VA, Barmin VV. Segmentectonomy in patients with malignant tumors of the lung. *P.A. Herzen Journal of Oncology*. 2017; 6(5):87–95. (In Russ.). https://doi.org/10.17116/onkolog20176587-95
6. Ismagilov AKh, Asnina NG, Azarov GA. Sentinel lymph node biopsy: history and current concepts. *Tumors of female reproductive system*. 2018; 14(1):38–46. (In Russ.). https://doi.org/10.17650/1994-4098-2018-14-1-38-46
7. Manikhas GM, Martynyuk VV, Zin'kevich MV. Biopsy of the signal lymph node with melanoma of the skin of the limbs and trunk. *Vestnik Sankt-Peterburgskoy gosudarstvennoy meditsinskoy akademii imeni I.I. Mechnikova*. 2008; (1):107–110. (In Russ.).
8. Ettinger DS, Wood DE, Aggarwa l C, Aisner DL, Akerley W, Bauman JR, et al. Non-Small Cell Lung Cancer, Version 1.2020, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2019; 17(12):1464–1472.https://doi.org/10.6004/jnccn.2019.0059
9. Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013; 143(5 Suppl):e211S–e250S.https://doi.org/10.1378/chest.12-2355
10. Tiffet O, Perrot JL, Gentil-Perret A, Prevot N, Dubois F, Alamartine E, et al. Sentinel lymph node detection in primary melanoma with preoperative dynamic lymphoscintigraphy and intraoperative gamma probe guidance. *Br J Surg*. 2004; 91(7):886–92.https://doi.org/10.1002/bjs.4548
11. Usman Ali M, Miller J, Peirson L, Fitzpatrick-Lewis D, Kenny M, Sherifali D, et al. Screening for lung cancer: A systematic review and meta-analysis. *Prev Med*. 2016; 89(3):301–314. https://doi.org/10.1016/j.ypmed.2016.04.015
12. Wishart GC, Loh SW, Jones L,Benson JR. A feasibility study (ICG-10) of indocyanine green (ICG) fluorescence mapping for sentinel lymph node detection in early breast cancer. *Eur J Surg Oncol*. 2012; 38(8):651–6.https://doi.org/10.1016/j.ejso.2012.05.007
13. Yamashita SI, Tokuishi K, Anami K, Miyawaki M, Moroga T, Kamei M, et al. Video-assisted thoracoscopic indocyanine green fluorescence imaging system shows sentinel lymph nodes in non-small-cell lung cancer. *J Thorac Cardiovasc Surg*. 2011; 141(1):141–4.https://doi.org/10.1016/j.jtcvs.2010.01.028

Information about the authors:

Vladislav V. Kovalenko — Senior Lieutenant of medical service, clinical resident of the Department (clinic) hospital surgery, Military Medical Academy named after S.M. Kirov, Russian Defense Ministry, Saint-Petersburg, Russia.

Oleg V. Barinov — Colonel of the Medical Service, ScD, Associate Professor, Deputy Head of the Department of Hospital Surgery, Military Medical Academy named after S.M. Kirov, Russian Defense Ministry, Saint-Petersburg, Russia.

Evgenij E. Fufaev — Lieutenant Colonel of Medical Service, PhD, Associate Professor of the Department of Hospital Surgery, Military Medical Academy named after S.M. Kirov, Russian Defense Ministry, Saint-Petersburg, Russia — **responsible for contacts, fufaev.jj@gmail.com**, ORCID: 0000-0003-1786-0560, eLibrary SPIN: 5758-2364

Ivan V. Dmitrochenko — Captain of the Medical Service, Senior Resident of the Surgical Department (Clinic) of Hospital Surgery, Military Medical Academy named after S.M. Kirov, Russian Defense Ministry, Saint-Petersburg, Russia.

Igor' V. Kurakevich — Major of Medical Service, Senior Resident of Surgical Department, Branch No. 1 of the Federal State-owned institution "439th Military Hospital" of the Ministry of Defense of the Russian Federation, Sergeyevka village, Border District, Primorsky Krai, Russia.

The authors declare no conflicts of interest.
The study was not sponsored.
Received 25.05.2022

Treatment of non-small cell lung cancer using radiation therapy

UDK 616-006.699
DOI: 10.53652/2782-1730-2022-3-2-18-24

Gevorkian A.R., Smolin A.V.

Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia

Abstract. The article is devoted to the use of a combination of systemic and radiation therapy in patients with locally advanced non-small cell lung cancer (NSCLC). The high risk of latent metastasis in this category of patients sets the prerequisites for active research of the combination of radiation therapy and systemic treatment worldwide. The article presents the results of clinical studies aimed to find the most optimal ratio of efficacy and safety of the chemotherapeutic component of chemoradiotherapy (CRT). According to the results of the research, the authors prefer the use of schemes based on platinum doublets. The article discusses the evaluation of the effectiveness of chemoradiotherapy with escalation of the radiation dose to the tumor within the framework of the concept of a personalized approach to therapy of patients with NSCLC. The article also pays attention to the description of new possibilities for RT intensification and the introduction of new RT methods, the use of which became possible with the introduction of innovative linear accelerators. The results of comparing the effectiveness of combined chemoradiotherapy with immunotherapy and chemoradiotherapy alone in patients with lung NSCLC are presented.

Keywords: lung cancer, radiation therapy, chemoradiotherapy, chemotherapy, immunotherapy.

Introduction. Lung cancer is one of the frequently diagnosed types of malignant neoplasms with a high mortality rate [1], mainly occurring in men and taking the third place in the morbidity structure among women. Non-small cell lung cancer (NSCLC) is the most common histological subtype, accounting for about 85% of all lung cancer cases.

In recent years, there has been a tendency to an increase in the incidence of disseminated forms of lung cancer due to the lack of adequate screening methods allowing to detect the disease at early, potentially curable stages [2, 3]. In 70% of cases, the disease is represented by locally disseminated or metastatic process. According to published literature, more than half of patients die in the first year after diagnosis [4]. It should also be noted that a significant number of patients are contraindicated for surgical treatment because of concomitant pathology associated with older age. Therefore, conservative therapy in the form of radiotherapy and/or systemic therapy remains the only treatment option for these patients, which is currently considered the standard to improve both local control and overall survival [5].

In a number of cases, radiation therapy (RT) is an alternative method that is comparable in effectiveness to surgical treatment. In locally disseminated stages of the disease, there is currently no alternative to radiotherapy. However, despite the efficiency of this method, it is clearly insufficient for effective disease control. The main reason is a high risk of "hidden" metastases that is why the world's leading scientists are making efforts to improve the efficiency of RT. There are several main approaches. One of the most important is the combination of radiation and chemotherapy. Chemotherapy is combined with RT to enhance the local effect and reduce the risk of distant metastasis.

Material and methods. Over the past decade, data from several studies of chemoradiotherapy (CRT) for unresectable NSCLC have been published. A research team led by Ming-SzuHung conducted a meta-analysis of 13 studies investigating the efficacy of CRT versus RT.

A total of 1,936 patients with unresectable, inoperable stage III NSCLC were included in the meta-analysis, of whom 975 received RT alone and 961 received CRT. Age ranged from 54 to 77 years. At 1 and 2 years after treatment, pooled data indicated that patients who received CRT had higher overall survival rates (hazard ratio (HR) 0.72; 95% confidence interval (CI) 0.62-0.84; p<001; 1 year: HR 0.67; 95% CI 0.54-0.84; p<001; 2 year: OR 0.57; 95% CI 0.45-0.73; p<001), progression-free survival (PFS) (HR 0.73; 95% CI 0.60-0.89; p=002; 1 year: HR 0.36; 95% CI 0.24-0.53; p<001; 2 year: HR 0.38; 95% CI 0.23-0.63; p<001) [6].

At present, the most effective chemotherapy regimen has not been determined. Studies aimed at finding the optimal ratio of efficacy and safety of the chemotherapeutic component of CRT are in ongoing.

The use of platinum-based doublet regimens is preferable. For example, two meta-analyses published 11 years apart demonstrated a benefit of platinum-based combinations with RT in reducing the risk of mortality from RT by nearly 2-fold compared with other regimens (30% versus 18%) and in increasing 2-year survival by 4% [7, 8, 9].

In 2020, a group of scientists led by Masafumi Yamaguchi conducted a study to evaluate the efficacy of simultaneous CRT with carboplatin and vinorelbine in elderly patients with locally disseminated NSCLC. This multicenter phase II study included patients with inoperable stage I-III NSCLC who were ≥70 years old. Patients received carboplatin (AUC 2) and vinorelbine (15 mg/m2) on days 1, 8, 22, and 29 simultaneously with RT (2.0 Gy/day, 30 fractions, total focal dose (TDF) 60 Gy). The primary endpoint was objective response rate. The secondary endpoints were progression-free survival, overall survival, and complication rate.

50 patients (42 men and 8 women) were included in the study. The mean age was 77 years (range, 70-89 years) and clinical stage I/II/III in 3/7/40, respectively. 47 patients completed their planned treatment. Complete response was achieved in 4 patients, partial response in 31, disease stabilization in 12, and disease progression in 3 patients, giving an objective response rate of 70% (95% confidence interval: 55.4-82.1). Frequent adverse events of high grade 3 or higher were hematologic, but no treatment fatalities were noted. Median and 2-year progression-free survival (PFS) were 8.4 months and 21.1% (95% confidence interval: 9.5-32.7%), respectively, whereas median and 2-year overall survival were 15.4 months and 41.1% (95% confidence interval: 27.0-55.2), respectively. It was concluded that simultaneous CRT with carboplatin and vinorelbine showed acceptable objective response rates and safety in elderly patients [10].

Worthy of note is the work of T.M. Borisova et al. who aimed to evaluate the overall efficacy of CRT with radiation dose escalation on the tumor within the concept of a personalized approach to therapy of NSCLC patients.

Under this study, 51 patients with inoperable stage III NSCLC were treated: stage IIIA — 15; IIIB — 36 patients. Treatment was performed using a simultaneous integrated booster - SIB-IMRT, with escalation of radiation dose to areas of hypermetabolism by PET/CT to BED10=70-74 Gy in 22-25 fractions. At the same time, chemotherapy was conducted according to the scheme: paclitaxel 175 mg/m2 + carboplatin AUC 5.0 with a consolidation course after the end of CRT.

With a median of 42 months, overall 1-, 2-, and 3-year survival rates in the group of patients who received CRT were 80.8% (95% CI 69.7-93.7); 64.6% (95% CI 50.4-82.9); and 54.2% (95% CI 38.3-76.9), respectively. 1-, 2-, and 3-year progression-free survival: 77.3% (95% CI 56.7-90.2); 48.7% (95% CI 32.3-70.1); 29.2 (95% CI 18.7-43.2), respectively [11].

Along with the study of the chemotherapeutic component, the possibility of intensifying RT and the introduction of new methods of RT, the use of which has become available with the emergence of innovative linear accelerator, are being investigated. High-tech RT using simultaneous integrated booster (SIB-IMRT) is capable of delivering a high dose to the tumor. Dosimetric studies have shown that the use of SIB-IMRT in patients with unresectable stage IIIA/IIIB NSCLC compared to the standard treatment regimen increased the local dose to the tumor, while there were no significant dose changes to critical structures [9].

Iqbal M.S. et al. conducted a phase II study of RT in hypofractionation mode, with simultaneous full-dose chemotherapy in locally advanced NSCLC. 92 patients received RT to an TFD of 58.8 Gy (21 fractions) (a single focal dose (SFD) of 2.8 Gy for 4 weeks) with two cycles of cisplatin at a dose of 80 mg/m2 on days 1 and 22 and vinorelbine at 25 mg/m2 on days 1, 8, 22 and 29 of RT. Two patients failed to complete RT, and 24% of patients failed a second course of chemotherapy due to toxic reactions. The median survival was 25 months (95% CI 14-36) and the median overall survival (OS) was 38 months (95% CI 27-49) [12].

In another study by Iqbal M.S. [13] presented the experience of treatment of 100 patients with hypofractionated dose (TFD 55 Gy (20 fractions) for 4 weeks with SFD 2.75 Gy), combined CRT in SOCCAR regimen [14] (simultaneous CRT: cisplatin 20 mg/m2 on days 1-4 and 16-19 with vinorelbine 15 mg/m2 on days 1, 6, 15 and 20). Then 4 weeks later, 2 more cycles of cisplatin 80 mg/m2 on days 1 and vinorelbine 25 mg/m2 on days 1 and 8 were given 3 weeks apart. There was one fatality due to the toxicity, and 2 patients developed grade 4 toxicity. The median PFS was 23.4 months and the OS was 43.4 months. All 4 cycles of chemotherapy were completed in 73% of patients. Both the original SOCCAR study and this work show that hypofractionated CRT is safe and provides a good result [13].

Hypofractionated RT — the use of a higher dose of radiation in fewer fractions — is being applied more and more often in the treatment of tumors of various localizations. In recent years, the method has shown its safety and clear advantages over classical fractionation.

A group of authors led by A. Patibandla conducted a study, the purpose of which was to perform CRT in patients with stage III NSCLC in hypofractionation mode. (NSCLC; SOCCAR regimen): TFD 55 Gy (20 fractions) for 26 days with accompanying chemotherapy (cisplatin and vinorelbine) [14].

A total of 163 patients were included in the study. Only 3% did not receive planned RT, and 76% received both cycles of concurrent chemotherapy. There were no treatment-related deaths within 30 or 90 days. Mean overall survival was 31.2 months; 1-, 2-, and 3-year survival rates were 75, 56, and 45%, respectively.

The number of patients enrolled in the study was similar to the RTOG 0617 control group. The median survival of 31.2 months in this study was achieved by using RT in the classical fractionation mode (2 Gy per fraction), up to a total focal dose of 60-66 Gy. The median PFS in the RTOG 0617 control group was 28.7 months [15]. The median PFS was 26.8 months in the PROCLAIM study group [16] and 29.1 months in the PACIFIC control group [17].

Expanding the possibility of applying CRT to patients with a relatively low general somatic status is an actual problem. In standard clinical practice, these patients are prescribed sequential CRT, the effectiveness of which is inferior to concomitant CRT. In a phase III study, NanBi et al. evaluated the efficacy and safety of concurrent CRT in patients with an ECOG score of 2. In the study, patients received concurrent EP (etoposide + cisplatin) / PC (paclitaxel + carboplatin) chemotherapy with intensity-modulated RT (IMRT) or three-dimensional conformal external beam RT (3D-CRT).

A total of 71 ECOG 2 patients were included in the study. Forty-six (64.8%) patients were treated with IMRT. The median overall survival (OS) and progression-free survival in ECOG 2 patients was 16.4 months and 9 months, respectively. There were no differences in treatment progression and toxicity between ECOG 2 patients and ECOG 0-1 patients. In the ECOG 2 group (31 patients in the EP group and 40 patients in the PC group), median OS and 3-year OS were 15.7 months and 37.5% for the EP group and 16.8 months and 7.5% for the PC group, respectively (p=0.243). The incidence of radiation pneumonitis ≥3 was higher in the PC group (17.5% vs 0.0%, p=0.014) with 5 deaths associated with radiation pneumonitis, while the incidence of grade 3 esophagitis was numerically higher in the EP group (25.8% vs 10.0%, p=0.078).

It was concluded that concomitant CRT provided ECOG 2 patients with a promising outcome with acceptable toxicity. EP may be superior to PC in terms of safety profile for ECOG 2 patients [18].

Undoubtedly, the combination of radiation and chemotherapy has shown high results. However, modern science does not stand still, and in recent years a study of combinations of CRT with immunotherapy in NSCLC has begun. Radiation therapy can increase antigen presentation, which in turn enhances the effect of RT. Haili Qian et al. conducted a meta-analysis to compare the efficacy of combined CRT with immunotherapy and CRT alone in patients with NSCLC.

At present, the most effective chemotherapy regimen has not been determined. Studies aimed at finding the optimal ratio of efficacy and safety of the chemotherapeutic component of CRT are in ongoing

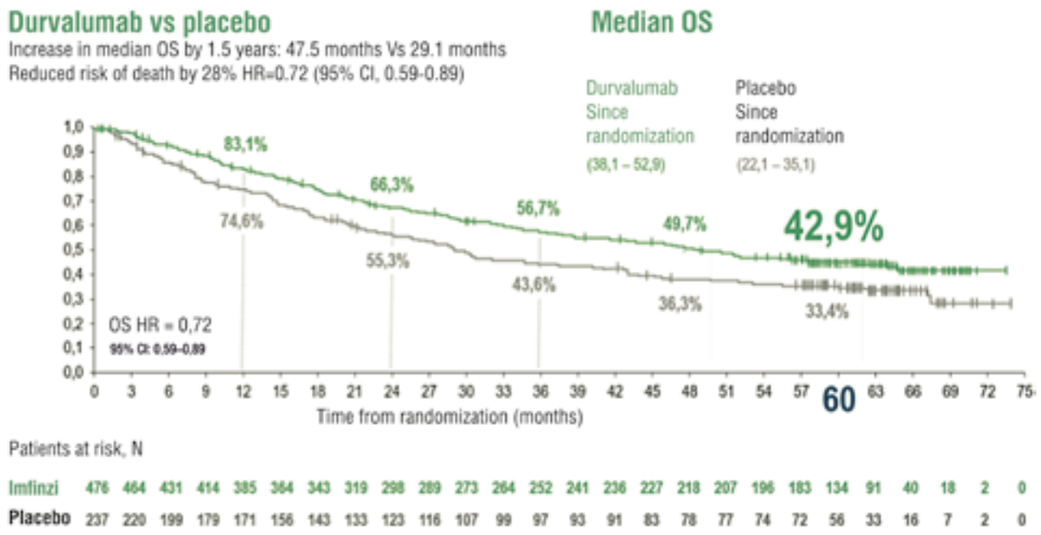


Fig. 1. PACIFIC study: updated 5-year overall survival

A total of 7 studies were included in the analysis. It showed that compared with CRT alone, immunotherapy combined with CRT could improve 2-year overall survival (HR 2.45; 95% CI 1.60-3.75; p<0.001) but not 2-year progression-free survival (HR 1.81; 95% CI 0.61-5.36; p=0.284). Specifically, early (HR 3.32; 95% CI 1.38-7.95; p<0.01) but not disseminated (HR 3.75; 95% CI 0.96-14.68; p=0.057) patients with NSCLC were likely to have better outcomes.

The authors concluded that immunotherapy combined with CRT can delay NSCLC progression and improve patient survival, the benefits being even greater in patients with early-stage NSCLC [19]. Final confirmation of the efficacy of immunotherapy in patients with inoperable stage III NSCLC after CRT was obtained in the PACIFIC trial.

In a placebo-controlled phase III study on PACIFIC patients with inoperable stage III NSCLC without disease progression after concurrent CRT, durvalumab significantly improved overall survival (OS) (HR 0.68; 95% CI 0.53-0.87; p=0.00251; data cutoff March 22, 2018) and PFS (HR 0.52; 95% CI 0.42-65; p<0.0001; February 13, 2017).

A total of 709 of 713 randomized patients received durvalumab (n/N=473/476) or placebo (n/N=236/237). As of March 20, 2020, median follow-up = 34.2 months; range: 0.2-64.9, updated OS (HR 0.71; 95% CI 0.57-0.88) and PFS (HR 0.55; 95% CI 0.44-0.67) remained consistent with the primary analyses. A median OS was achieved for durvalumab (47.5 months; placebo, 29.1 months). The 4-year OS rates were 49.6% versus 36.3% for durvalumab compared with placebo, and the 4-year PFS rates were 35.3% versus 19.5%, respectively.

The findings demonstrate a prolonged progression-free survival and a consistent overall survival benefit with the use of durvalumab after CRT. We estimated that 49.6% of patients who received immunotherapy remained alive for 4 years (placebo, 36.3%) and 35.3% remained alive and progression-free (placebo, 19.5%) [20].

In 2021, updated data were published estimating a 5-year OS (Fig. 1).

After 5 years, 42.9% of patients in the group receiving durvalumab were alive, compared with 33.4% in the control group [21].

Radiation therapy, even in metastatic neoplasms, can lead to the development of abscopal effects. The abscopal effect was described more than 50 years ago. It is a phenomenon in which RT contributes to the regression of metastatic foci distant from the site of exposure. It is characterized as a rare, unexplained phenomenon in post-RT patients. The mechanisms underlying it are still not fully understood. According to some scientists, it is most likely related to the systemic immune system response that occurs under the influence of RT [22]. Given the synergism of RT and immunotherapy, there are theoretical prerequisites for the integration of RT in the treatment of metastatic NSCLC.

This was the approach studied in the PEMBRO-RT and MDACC studies. Patients with metastatic NSCLC and at least one unexposed lesion were included in the studies to monitor objective responses. In the PEMBRO-RT study, patients had previously received chemotherapy, whereas in the MDACC study, patients may have been previously treated or were newly diagnosed. In the PEMBRO-RT study, patients were randomized (1:1) and stratified by smoking status (<10 versus ≥10 years of smoking). In the MDACC study, patients were included in one of two cohorts and distributed randomly (1:1). In both studies, pembrolizumab was given intravenously (200 mg every 3 weeks) simultaneously with or without RT. In the PEMBRO-RT study, the first dose of pembrolizumab was administered consecutively, less than 1 week after the last RT dose (24 Gy in 3 fractions), whereas in MDACC pembrolizumab was administered simultaneously with the first RT dose (50 Gy in 4 fractions or 45 Gy in 15 fractions). The endpoints for this pooled analysis were best objective response rate outside the radiation field (abscopal response rate (ARR)), abscopal control rate (ACR), ARR after 12 weeks, ACR after 12 weeks, progression-free survival, and overall survival. After analyzing the studies, there was potential benefit in the combination treatment group. However, because of the small sample size of each study, differences in response rates and outcomes did not reach statistical significance, but remained clinically significant. Therefore, Willemijn T. performed a pooled analysis of both studies to determine whether RT in combination with immunotherapy improves treatment outcomes in patients with metastatic NSCLC.

A total of 148 patients were included in the pooled analysis, of which 76 received pembrolizumab and 72 received pembrolizumab in combination with RT. The median follow-up for all patients was 33 months (32.4-33.6). Baseline factors did not differ between treatment groups, including subgroups of patients who did not differ in PD-L1 status and volume of metastatic lesion. The most common radiation zones were lung metastases (28 of 72 (39%)), intrathoracic lymph nodes (15 of 72 (21%)), and a primary focus in the lung (12 of 72 (17%)). The ARR was 19.7% (15 of 76) with pembrolizumab versus 41.7% (30 of 72) with pembrolizumab in combination with RT (HR 2.96; 95% CI 1.42-6.20; p=0.0039); and ACR was 43.4% (33 of 76) with pembrolizumab compared with 65.3% (47 of 72) with pembrolizumab plus RT (HR 2.51; CI 1.28-4.91; p=0.0071). The median PFS was 4.4 months (IQR 2.9-5.9) with pembrolizumab alone compared to 9 months (6.8-11.2) of pembrolizumab plus RT (HR 0.67; 95% CI 0.45-0.99; p=0.045), and the median OS was 8.7 months (6.4-11.0) in the pembrolizumab group compared to 19.2 months (14.6-23.8) with pembrolizumab plus RT (HR 0.67; CI 0.54-0.84; p=0.0004). There were no new treatment safety concerns in the pooled analysis. The authors concluded that the addition of RT to pembrolizumab immunotherapy significantly improved response rates in patients with metastatic NSCLC [23].

Conclusions. Integration of RT in the treatment of metastatic NSCLC seems very promising, and further research in this direction is required.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018; 68(6):394–424. https://doi.org/10.3322/caac.21492
2. Henschke CI; I-ELCAP Investigators. CT screening for lung cancer: update 2005. *Surg Oncol Clin N Am*. 2005; 14(4):761–76. https://doi.org/10.1016/j.soc.2005.07.002
3. Smith RA, Cokkinides V, Eyre HJ. American Cancer Society guidelines for the early detection of cancer, 2006. *CA Cancer J Clin.* 2006; 56(1):11–25; quiz 49–50. https://doi.org/10.3322/canjclin.56.1.11
4. Kaprin AD, Starinskij VV, Petrova GV, editors. *Sostoyaniye onkologicheskoy pomoshchi naseleniyu Rossii v 2014 g.* Moscow: MNIOI im. P.A. Gertsena; 2015. 236 p. (In Russ.). https://www.oncology.ru/service/statistics/condition/2014.pdf
5. Chargari C, Soria JC, Deutsch E. Controversies and challenges regarding the impact of radiation therapy on survival. *Ann Oncol*. 2013; 24(1):38–46. https://doi.org/10.1093/annonc/mds217
6. Hung MS, Wu YF, Chen YC. Efficacy of chemoradiotherapy versus radiation alone in patients with inoperable locally advanced non-small-cell lung cancer: A meta-analysis and systematic review. *Medicine (Baltimore)*. 2019; 98(27):e16167. https://doi.org/10.1097/MD.0000000000016167
7. Marino P, Preatoni A, Cantoni A. Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in stages IIIa and IIIbnon-small cell lung cancer. A meta-analysis. *Cancer*. 1995; 76(4):593–601. https://doi.org/10.1002/1097-0142(19950815)76:4<593::aid-cncr2820760409>3.0.co;2-n
8. Aupérin A, Péchoux CL, Pignon JP, Koning C, Jeremic B, Clamon G, et al. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-smallcell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. *Ann Oncol.* 2006; 17(3):473–83. https://doi.org/10. 10.1093/annonc/mdj117
9. Turner LM, Howard JA, Dehghanpour P, Barrett RD, Rebueno N, Palmer M, et al. Exploring the feasibility of dose escalation positron emission tomography-positive disease with intensity-modulated radiation therapy and the effects on normal tissue structures for thoracic malignancies. *Med Dosim*. 2011; 36(4):383–8. https://doi.org/10. 10.1016/j.meddos.2010.09.007
10. Yamaguchi M, Hirata H, Ebi N, Araki J, Seto T, Maruyama R, et al. Phase II study of vinorelbine plus carboplatin with concurrent radiotherapy in elderly patients with non-small cell lung cancer. *Jpn J Clin Oncol.* 2020; 50(3):318–324. https://doi.org/10.1093/jjco/hyz179
11. Borisova TN, Fedorova AA, Nazarenko AV, Tkachev SI, Laktionov KK, Breder VV, et al. High-Tech Radiation Therapy with Local Dose Escalation in Chemoradiotherapy of Patients with Non-Small Cell Lung Cancer Inoperable III Stage. *Journal of oncology: diagnostic radiology and radiotherapy.* 2019; 2(3):12–20. (In Russ.). https://doi.org/10.37174/2587-7593-2019-2-3-12-20
12. Iqbal MS, McMenemin R, Greystokec A. Hypofractionated chemoradiotherapy for locally advanced non-small cell lung cancer: Is split-dose chemotherapy safer than full dose chemotherapy? *Radiother Oncol.* 2020; 154:E13. https://doi.org/10.1016/j.radonc.2020.06.020

13. Iqbal MS, Vashisht G, McMenemin R, Atherton P, McDonald F, Simmons T, et al. Hypofractionated concomitant chemoradiation in inoperable locally advanced non-small cell lung cancer: a report on 100 patients and a systematic review. *Clin Oncol (R Coll Radiol)*. 2019; 31(2):e1–e10. https://doi.org/10.1016/j.clon.2018.10.006
14. Maguire J, Khan I, McMenemin R, O-Rourke N, McNee S, Kelly V, et al. SOCCAR: a randomised phase II trial comparing sequential versus concurrent chemotherapy and radical hypofractionated radiotherapy in patients with inoperable stage III non-small cell lung cancer and good performance status. *Eur J Cancer*. 2014; 50(17):2939–49. https://doi.org/10.1016/j.ejca.2014.07.009
15. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol*. 2015; 16(2):187–99. https://doi.org/10.1016/S1470-2045(14)71207-0
16. Senan S, Brade A, Wang L, Vansteenkiste J, Dakhil S, Biesma B, et al. PROCLAIM: randomized phase III trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced non-squamous non-small-cell lung cancer. *J Clin Oncol.* 2016; 34(9):953–62. https://doi.org/10.1200/JCO.2015.64.8824
17. Gray JE, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Three-Year Overall Survival With Durvalumab After Chemoradiotherapy in Stage III NSCLC-Update From PACIFIC. *J Thorac Oncol.* 2020; 15(2):288–293. https://doi.org/10.1016/j.jtho.2019.10.002
18. Bi N, Liu L, Liang J, Wu S, Chen M, Lv C, et al. Efficacy and safety of concurrent chemoradiotherapy in ECOG 2 patients with locally advanced non-small-cell lung cancer: a subgroup analysis of a randomized phase III trial. *BMC Cancer*. 2020; 20(1):278. https://doi.org/10.1186/s12885-020-06780-x
19. Qian H, Wang H, Guan X, Yi Z, Ma F. Adoptive immunotherapy combined chemoradiotherapy for non-small-cell lung cancer: a meta-analysis. *Anticancer Drugs.* 2016; 27(5):433–8. https://doi.org/10.1097/CAD.0000000000000346
20. Faivre-Finn C, Vicente D, Kurata T, Planchard D, Paz-Ares L, Vansteenkiste JF, et al. Four-Year Survival With Durvalumab After Chemoradiotherapy in Stage III NSCLC-an Update From the PACIFIC Trial. *J Thorac Oncol*. 2021; 16(5):860-867. https://doi.org/10.1016/j.jtho.2020.12.015
21. Spigel DR, Faivre-Finn C, Gray JE, Vicente D, Planchard D, Paz-Ares LG, et al. Five-year survival outcomes with durvalumab after chemoradiotherapy in unresectable stage III NSCLC: An update from the PACIFIC trial. *Journal of Clinical Oncology.* 2021; 39(15_suppl):8511–8511. https://doi.org/10.1200/JCO.2021.39.15_suppl.8511
22. Denisova ES, Laktionov KK, Borisova TN, Ardzinba MS, Fedorova AA, Yudin DI, et al. Abscopal effect in a patient with metastatic NSCLC following a course of radiation therapy to the brain. *Medical Council.* 2020; (20):188-193. (In Russ.). https://doi.org/10.21518/2079-701X-2020-20-188-193
23. Theelen WSME, Chen D, Verma V, Hobbs BP, Peulen HMU, Aerts JGJV, et al. Pembrolizumab with or without radiotherapy for metastatic non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Respir Med*. 2021; 9(5):467-475. https://doi.org/10.1016/S2213-2600(20)30391-X

Information about the authors:

Andrej R. Gevorkian — radiotherapist, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia — **responsible for contacts**, **dr.gevorkian@mail.ru**, ORCID: 0000-0001-6665-4814; eLibrary SPIN: 2222-56167

Aleksej V. Smolin — MD, PhD, Chief of the Center for radiology, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

The authors declare no conflicts of interest.
The study was not sponsored.
Received 31.05.2022

Application of activated conditioned plasma in patients with macular rupture

UDK 611.018.54
DOI: 10.53652/2782-1730-2022-3-2-26-34

Pavlov V.A., Kurnosov V.E., Zinovyev S.A., Kapatsina A.A., Utkina E.E.

Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia

Abstract. ***Objective.*** To evaluate and summarize the results, as well as to conduct a comparative analysis of the treatment of patients with macular rupture with autoplasm, using a Rotofix 32A Centrifuge and Arthrex ACP systems to obtain autologous conditioned plasma (ACP) with previously used surgical methods.
Material and methods. The study conducted a comparative analysis of the results of treatment of patients with macular rupture, with a corrected visual acuity of more than 0.08 (according to the Golovin–Sivtsev table). Group 1 (prospective analysis) included the results of treatment using peeling of the inner boundary membrane with a gas/air tamponade in combination with the application of ACP (4 eyes, 4 patients). In the 2nd group (retrospective analysis of the medical history), surgical treatment was limited to the peeling of the inner boundary membrane with a gas/air tamponade (8 eyes, 8 patients). The parameters were analyzed after 3.0±0.5 and 6.0±0.5 months with assessment of maximum corrected visual acuity (MCOZ), optical coherence tomography (OCT), color photography. Closure of the macular gap was assessed at 6 months of follow-up when comparing the groups.
Results. No complications were detected in both groups during the observation period. According to visometry and OCT data, the best functional results were obtained in group 1. The average visual acuity after 6 months was 0.4±0.1.
Conclusion. The study found that the use of the peeling of the inner boundary membrane with gas/air tamponade and the use of platelet-derived mass increased the probability of rupture closure.

Keywords: autologous plasma, macular rupture, platelets, cystic retinal edema, surgical treatment.

Introduction. Vitreomacular interface pathology has recently occupied one of the leading positions in the structure of visual impairment in adults [1, 2]. Considering the active introduction of optical coherence tomography into clinical diagnostics, macular holes as a central visual impairment are revealed increasingly more frequently. Macular hole is a defect of the neurosensory part of the retina in the foveolar zone with a tractional component. This is visualized by biomicroscopy on the fundus of the eye as a small round or oval macular defect, hence the second name of the disease - macular hole. Its prevalence is up to 3%, according to different literature data [3]. The incidence of this type of pathology is higher among females

[4]. Asymptomatic course at an early stage of the disease is a complicating factor for timely recognition. Absence of modern optical coherence tomography scanners at the stage of outpatient care, garrison and military hospitals leads to late diagnosis as early signs may be mistaken for age-related macular degeneration (from our own observations). The formation of a hole to the retinal pigment epithelium is accompanied by a marked decrease in visual acuity, metamorphopsia, and the appearance of central positive scotoma [5].

German ophthalmologist N. Kparr first described macular hole in 1869, then in 1900 H. Kuhnt considered this pathology as a degenerative process involving vascular disorders accompanied by atrophic processes in the retina, which lead to the formation of a hole. The current classification was proposed in 1995 by J.D. Gass, he also considered the theory of macular interface pathology development [6]

The central zone of the retina (macula) is the largest concentration of photoreceptor cells (rods and cones). It is this area of the retina that is the most important in the visual act, it provides pattern vision.

The space between the retina and the lens is filled by the vitreous body, a transparent gel-like structure occupying 4/5 of the eyeball volume. The vitreous body adjoins the retina, and is most tightly connected to it in the projection of the macular zone. The vitreous body undergoes degenerative changes due to natural age-related causes; it liquefies and detaches from the retina. In the pathological process of detachment, it has a pronounced tractional effect on the retina in its central part and provokes the formation of a defect in the macular zone. Vitreoretinal traction plays the leading role in the pathogenesis of macular holes. Considering the traction theory, the classification of macular holes used in modern clinical practice was developed with division into the following stages:

- 1a — can be described with the appearance of a "yellow spot" in the foveola and changes in the depth of the foveola;
- 1b — one of the signs is the formation of a "yellow ring" with disappearance of the foveolar reflex;
- 2 — in redless light described as formation of a through retinal tear up to 400 μm in diameter with fixation of the posterior hyaloid membrane to the retinal surface;
- 3 — the perforated retinal defect expands in diameter and becomes more than 400 μm, the posterior hyaloid membrane fixation is preserved;
- 4 — this is a perforated retinal defect more than 400 μm in diameter with the posterior hyaloid membrane completely detached from the retinal surface.

With the introduction of optical coherence tomography (OCT) into ophthalmological practice, the understanding of the progression of this pathology has changed, making it possible to diagnose and document structural changes in the macular interface [7]. At the same time, the classification is complemented by OCT data.

At stage 1a, OCT-diagnostics reveals the following signs: changes in the contour and structure of foveolar depression, formation of a pseudocyst in the inner retinal layers, partial detachment of posterior hyaloid membrane fixed to the inner wall of the pseudocyst. These changes occur under the impact of vitreoretinal traction. On OCT-image it is possible to see that foveola profile is smoothed, neuroepithelium is locally detached from inner nuclear layer, forming a pseudocyst with an appearance of optically empty cavity (Fig. 1).

Stage 1b: further deformation of the profile and structure of the foveolar depression progresses. The pseudocyst expands in size and extends to the outer layer of the retinal neuroepithelium. The upper wall of the cyst ("lid") remains intact, the posterior hyaloid membrane is still attached to it (Fig. 2).

OCT-diagnostics at stage 2 reveals the following: deformation of the contour and structure of the macular zone of the retina, partial detachment of the "cap", with structural elements of the retina at adhesion of the posterior hyaloid membrane to its flap, formation of penetrating neuroepithelium defect with diameter less than 400 μm, in the nuclear layers cystic edema of the retinal tear edges is formed.

OCT-signs of stage 3: pronounced deformation of the foveolar depression profile, penetrating defect of retinal neuroepithelium over 400 μm in diameter, "cap" fixed to the fully detached posterior hyaloid membrane, thickness of retina in the area of tear edges increased along with progressing cystic edema, whereas the posterior hyaloid membrane was fixed to the optic nerve disc (Fig. 3).

Stage 4 on OCT is defined as follows: pronounced deformation of the contour and structure of the macular retinal zone, penetrating defect of neuroepithelium over 400 μm in diameter, with the outer nuclear layer, outer boundary membrane and junction line of outer and inner photoreceptor segments interrupted, retinal thickness at the edges of hole is increased due to cyst fusion, subretinal fluid accumulation is visualized under elevated edges of formed hole. The posterior hyaloid membrane is detached from the macula and from the optic nerve disc (may not be visible on optical section) (Fig. 4).

By etiology, there are: primary (idiopathic in the presence of vitreomacular traction), secondary (revealed due to eye trauma, against the background of complicated high degree myopia, previous ophthalmic surgical interventions, etc.). A traumatic macular hole of the retina is caused by a closed trauma to the eyeball (eye contusion) which leads to the rupture of the retina in its thinnest central part. Myopic macular hole occurs as a complication in

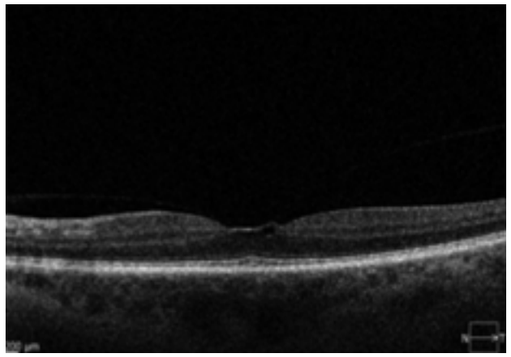


Fig. 1. Stage 1a of macular hole

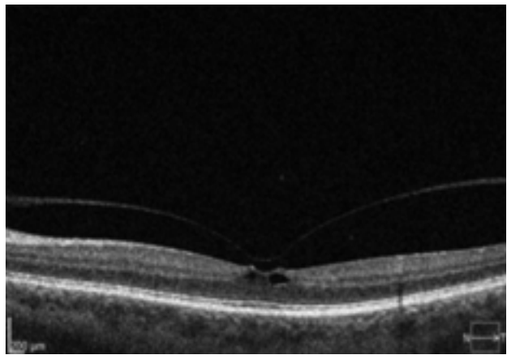


Fig. 2. Stage 1b of macular hole

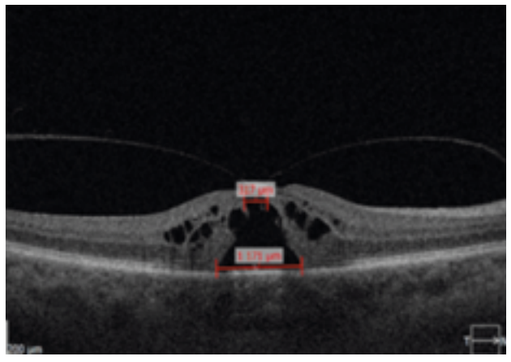


Fig. 3. Stage 3 macular hole

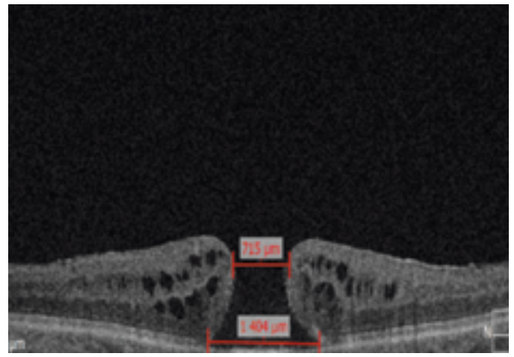


Fig. 4. Stage 4 of macular hole

high myopia and is the most severe type of macular hole in terms of the choice of surgical treatment tactics and the prognosis of visual function recovery, and it is also complicated by the development of retinal detachment. Postoperative macular hole occurs in less than 1% of patients who have undergone surgery for retinal detachment. Depending on the depth of the defect: penetrating holes, lamellar holes.

According to the size, the holes are divided into: small (less than 250 μm), medium (250-400 μm), and large (over 400 μm). Also devided according to the presence or absence of vitreomacular traction (VMT).

The choice of surgical treatment tactics is individual in each clinical case, taking into account the corresponding retinal changes according to the above classifications.

During the OCT, the retinal profile, the presence of epiretinal membranes, the horizontal slit at the level of the outer plexiform layer are assessed. Small optically empty cavities associated with edema are detected at the level of nuclear layers. Outer nuclear layer, outer boundary membrane, conjunction line of outer and inner segments of photoreceptors, pigment epithelium, choriocapillaries are not changed.

At this stage of modern vitreoretinal surgery development, only in 65% of cases the treatment of macular holes is successful. Many etiopathogenetic aspects of the process remain unresolved. The advisability of total removal of the internal boundary membrane (IBM) is quite debatable. The authors [5] suggest performing surgery with only removal of the adherent vitreous body without removing the IBM in the initial stages. At stages 3 and 4, the technique of using autologous blood to close penetrating defects has been popular for several years [2], however, the efficacy of this technique is a subject for further discussion. The main factor for the decision on surgical treatment tactics is the classification component of the

Table 1. Research groups of applied methods

Comparison parameters		Research groups	
		1st	1nd
Number of patients		4 patients (4 eyes)	8 patients (8 eyes)
Type of surgical intervention		IBM peeling with gas/air tamponade and ACP application	IBM peeling with gas/air tamponade
Visual acuity before surgical treatment (according to Golovin-Sivtsev table)		before 0,08±0,1	before 0,08±0,1
Visual acuity after surgical treatment (according to Golovin-Sivtsev table)	after 3,0±0,5 months	before 0,3±0,1	before 0,2±0,1
	after 6,0±0,5 months	before 0,4±0,1	0,3±0,1
Retinal thickness in the macular region before surgical treatment, μm		382±10 μm	377±10 μm
Statistically significant decrease in macular thickness, μm	after 3,0±0,5 months	327±20 μm	382±20 μm
	after 6,0±0,5 months	277±15 μm	282±15 μm

macular zone defect. Its basis makes it possible to determine the greatest expediency of this or another method of treatment at a certain stage of the disease.

One of the effective methods of treatment is therapy with activated plasma. Considering its autologous nature, this therapy is both an effective and safe method of treatment, that is why the indications for its application are expanding [8]. The specified techniques are applied not only in macular hole surgery, but also in regmatogenic retinal detachment, corneal pathologies, penetrating wounds of the eyeball [9-12].

Based on the various methods of obtaining autologous blood plasma (ABP), these preparations are classified into the following end products according to their cellular composition or fibrin content: Autologous Conditioned Plasma (ACP) and Platelet-Rich Plasma (PRP), which are currently used in various fields of medicine. In turn, PRP preparations are divided into pure PRP (Pure Platelet-Rich Plasma / P-PRP) and Plasma Rich Growth Factors (PRGF). A distinction is also made according to the leukocyte content between Pure Platelet-Rich Fibrin (P-PRF), Leukocyte-Platelet-Rich Fibrin (L-PRF) and Platelet-Rich Fibrin (Advanced / A-PRF) [13].

APC-products are a pool of growth factors that attract stem cells to the damage area and determine their further differentiation into a certain cell type.

The application of autoplasma treatment techniques is one of the areas of tissue engineering and cell therapy. The use of APC-therapy to accelerate bone and soft tissue growth has become a breakthrough in various surgical specialties of traumatology, sports medicine, dentistry, cosmetology and surgery. When choosing a protocol for plasma preparation, it is necessary to consider the mode and time of centrifugation, the presence

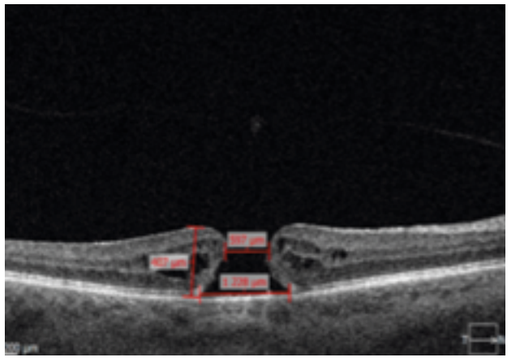


Fig. 5. Stage 4 macular hole in patient K.

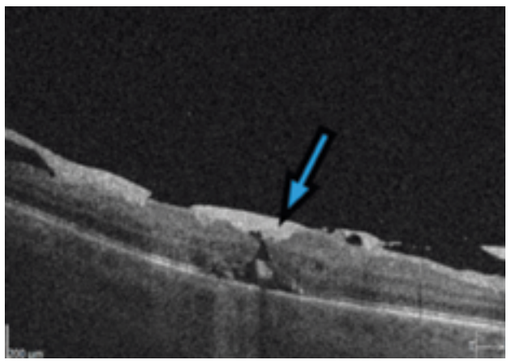


Fig. 6. The state of the macular hole one day after ACP application.

of anticoagulant and the method of plasma collection, giving preference to closed systems that allow to obtain "clean" APC with low immune activity, which is especially important in vitreoretinal surgery. Diseases associated with ocular surface lesions require correction of the local immune status, which may determine the possibility of using PRP [14]. Hole closure when using autoplasma occurs due to platelet retention in the rupture zone by the fibrin component. Then the process of retraction with subsequent compaction and fixation of platelet mass starts. As a result, a fibrin matrix is formed, which promotes cell migration of monocytes, fibroblasts and other cells actively participating in regenerative processes.

Purpose. To evaluate the results, generalize and systematize them, and conduct a comparative analysis of the treatment of patients with macular hole with the help of autoplasma using the Rotofix32A centrifuge and Arthrex ACP system for obtaining autologous conditioned plasma with previously used surgical methods.

Materials and Methods. Inclusion criteria for the study were patients of different age with idiopathic macular hole.

We analyzed the results of treatment of 12 patients (12 eyes) including 4 male patients aged 50.8 (44-58) years and 8 female patients aged 46.8 (38-60) years divided into 2 groups (Table 1).

Group 1 (prospective analysis) included the results of treatment of patients with macular hole who underwent ACP-plasma application technique (4 eyes, 4 patients). In the 2nd group (retrospective analysis of medical history) patients underwent the method of surgical treatment of retinal macular hole on the basis of IBM peeling with gas/air tamponade (8 eyes, 8 patients).

Both groups used analogous standard therapy, including local and systemic anti-inflammatory treatment. The average follow-up period was 6.0±0.5 months. Information on etiology, indications for treatment, best corrected visual acuity was collected. The baseline hole diameter at the level of retinal pigment epithelium (a) minimum diameter (b) was measured. The parameters were analyzed after 3.0±0.5 and 6.0±0.5 months with assessment of maximum corrected visual acuity (MCVA), OCT, and color photography. The risk of macular edema recurrence when comparing the groups was assessed at 6 months of follow-up.

Group 1 (ACP): baseline diameter 1100-1600 μm, minimum diameter 350-500 μm, visual acuity 0.08.

Group 2 (VS): base diameter 800-1100 μm, minimum diameter 350-500 μm, visual acuity 0.08-0.1.

In each group, the patients had a macular lesion requiring surgical intervention in one of the eyes. Four eyes (4 patients) received ACP application at the end of surgery. Native plasma of the patients, without preservatives, prepared 15 minutes before application was used.

In group 2, patients underwent removal of IBM in one of the eyes. Patients in both groups underwent subtotal vitrectomy with removal of the IBM and tamponade with an air/gas mixture according to the standard technique. Vitrectomy was performed using Constellation systems.

In the early postoperative period, all patients were advised to stay in a face-down position for 3 hours.

Results. The surgeries were performed without complications in all groups. Small retinal hemorrhages in the place of IBM capture with micropincer during maculorexis were observed in 5 (41,7%) eyes during surgical intervention. The hemorrhages resolved on their own without affecting the visual functions. The postoperative course was smooth. The long-term results of treatment were evaluated after 1, 3 and 6 months. The criterion for a positive anatomical effect was a complete closure of the hole edges according to OCT data and an increase in visual acuity.

In group 1 before surgery, the mean visual acuity was 0.08±0.1 according to the Golovin-Sivtsev table, which increased to 0.3±0.1 (p=0.005) after 3.0±0.5 months, to 0.4±0.1 after 6.0±0.5 months (p=0.005). The retinal thickness of the macular region before surgery was 382±10 μm. Statistically significant reduction in macular thickness to 327±20 μm (p=0.005) after 3.0±0.5 months, to 277±15 μm (p=0.005) after 6.0±0.5 months.

In group 2 before surgery, the mean visual acuity was 0.1±0.1 according to the Golovin-Sivtsev table, which increased to 0.2±0.1 (p=0.005) after 3.0±0.5 months, to 0.3±0.1 after 6.0±0.5 months (p=0.005). The thickness of the macular retina before surgery was 377±10 μm. Statistically significant decrease in macular thickness to 382±20 μm (p=0.005) after 3.0±0.5 months, to 282±15 μm (p=0.005) after 6.0±0.5 months.

After 1 month in group 1 patients 100% effect was achieved in all 4 cases (4 eyes). According to OCT data, the hole was closed with preservation of retinal layer structure. Visual acuity in this group increased on average from 0.1 to 0.4.

The dynamics of the postoperative course is presented by the example of patient K. (Fig. 5-8).

The arrow indicates the film of platelet plasma, under which the edges of the hole are partially elevated

The arrow indicates filling of the residual cavity with migrated cells. The edges of the hole adjoined the pigment epithelium

After 3 months all patients in group 1 showed no recurrence of macular holes according to OCT data, improvement of visual functions was achieved, retinal profile was restored. Group 2 also achieved closure of the rupture in the eyes, but with a smaller increase in visual acuity. At the control OCT the retinal edema at the site of the ruptures almost disappeared. In Group

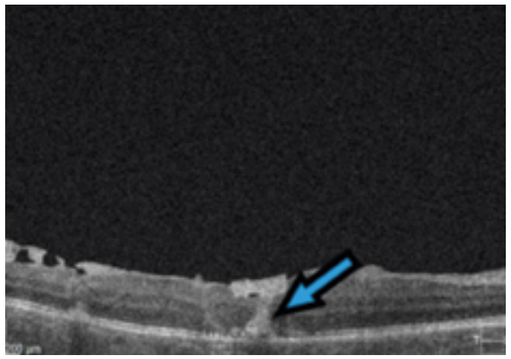


Fig. 7. Condition of the macular rupture on the 3rd day after the surgery.

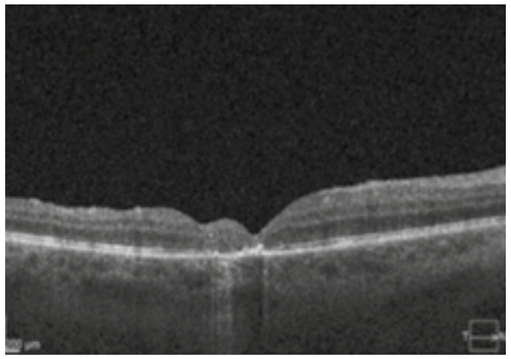


Fig. 8. Treatment result after 6 months with complete closure of the macular hole

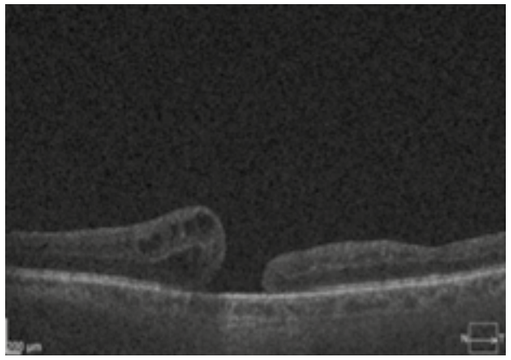


Fig. 9. Unclosed macular hole

2, there was one case of nonclosure of the macular hole (Fig. 9). The patient was operated again following the technique of Group 1 and the macular hole closure was achieved.

Conclusions. Based on our research we can make the following conclusions:

1. In penetrating macular hole surgery using ACP technique, closure was observed in the majority of patients; however, in the 2nd group of investigated patients, non-closure of macular hole was observed in one case.

2. The application of the IBM peeling and platelet mass technique improves the efficiency of surgery and increases the probability of hole closure.

Undoubtedly, the results are preliminary and further long-term follow-up is required.

References

1. Bikbov MM, Faizrakhmanov RR. Influence of antivasoprolipherative therapy on morphological and functional features classic choroidal neovascularization in patients with age-related macular degeneration. *Bulletin of the Russian military medical academy.* 2016; 54(2):111–115. (InRuss.). https://www.elibrary.ru/item.asp?id=26280201
2. Bikbov MM, Fayzrahmanov RR, Gil'manshin TR, Arslangareeva II. Morphological changes in the macular area at post-thrombotic maculopathy after intravitreal injection of a dexamethasone implant (evidence from 5 clinical cases). *Ophthalmology Journal.* 2016; 9(4):90–97. (In Russ.). https://doi.org/10.17816/OV9490-97
3. Bayborodov YV, Balashevich LI. Microinvasive surgical treatment of macular hole of stage I without vitrectomy under the intraoperative OCT control. *Fyodorov Journal of Ophthalmic Surgery*. 2017; (1):53–58. (In Russ.). https://doi.org/10.25276/0235-4160-2017-1-53-58
4. Shkvorchenko DO, Zakharov VD, Shpak AA, Krupina YeA, Pis'menskaya VA, Kakunina SA, et al. Nash opyt primeneniya bogatoy trombotsitami plasmy krovi v khirurgii makulyarnykh razryvov. *Modern technologies in ophthalmology.* 2016; (1):245–246. (In Russ.). https://www.elibrary.ru/item.asp?id=26334138
5. Bikbov MM, Fayzrakhmanov RR, Kalanov MR. Combined approach to the surgical treatment of patients with proliferative stage of diabetic retinopathy. *Saratov Journal of Medical Scientific Research*. 2017; 13(2):338–345. (In Russ.).
6. Gass JD. Reappraisal of biomicroscopic classification of stages of development of a macular hole. *Am J Ophthalmol.* 1995; 119(6):752–9. https://doi.org/10.1016/s0002-9394(14)72781-3
7. Fayzrakhmanov RR, Zainullin RM, Gilmanshin TR, Yarmukhametova AL. Kartirovaniye foveolyarnoy zony setchatki pri idiopaticheskom makulyarnom razryve. *Vestnik Orenburgskogo gosudarstvennogo universiteta.* 2014; 12(173):322–324. (In Russ.).
8. Fayzrahmanov RR, Krupina EA, Pavlovsiy OA, Larina EA, Suchanova AV, Karpov GO. Analysis of platelet-rich plasma obtained in various ways. Medline.ru. 2019; 20:363–372. (In Russ.).
9. Arsyutov DG. Use of platelet rich plasma, including autologous conditioned plasma, in the surgery of perforating eye injuries. *Saratov Journal of Medical Scientific Research*. 2020; 16(1):207–210. (In Russ.).
10. Arsiutov DG. Use of Autologous Conditioned Platelet Rich Plasma in the Surgery of Rhegmatogenous Retinal Detachment with Central and Peripheral Tears. *Acta biomedical scientifica*. 2019; 4(4):61–64. (In Russ.). https://doi.org/10.29413/ABS.2019-4.4.8
11. Shkvorchenko DO, Zakharov VD, KrupinaEA, Pismenskaya VA, Kakunina SA, Norman KS, et al. Surgical treatment of primary macular hole using platelet-rich plasma. *Fyodorov Journal of Ophthalmic Surgery.* 2017; (3):27–30. (In Russ.). https://doi.org/10.25276/0235-4160-2017-3-27-30
12. Tarabrina VA, Gavrilyuk IO, Churashov SV, Kulikov AN. The use of platelet-rich plasma on the experimental corneal erosion. *Modern technologies in ophthalmology*. 2020; (3):83–84. (In Russ.). https://doi.org/10.25276/2312-4911-2020-3-83-84
13. Achkasov EE, Bezuglov EN, Ul'yanov AA, Kurshev VV, Repetyuk AD, Egorova ON. Application platelet-rich plasma in clinical practice. *Biomedicine*. 2013; (4):46–59. (In Russ.).
14. Krupina EA, Fajzrahmanov RR, Pavlovsij OA, Larina EA, Suhanova AV, Karpov GO. Molecular and biological aspects of platelet-rich plasma therapies. *Bulletin of Pirogov National Medical & Surgical Center*. 2020; 15(3-2):80–85. (In Russ.). https://doi.org/10.25881/BPNMSC.2020.30.34.015

Information about the authors:

Viktor A. Pavlov — MD, Chief ophthalmologist of Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Vyacheslav E. Kurnosov — Head of Ophthalmic Department of Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia — **responsible for contacts**, **elaslav@yandex.ru**, ORCID: 0000-0003-3126-3316

Sergey A. Zinovyev — MD, Ophthalmic Department of Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Aleksandr A. Kapatsina — MD, Ophthalmic Department of Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Ekaterina E. Utkina — resident in Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

The authors declare no conflicts of interest.
The study was not sponsored.
Received 30.05.2022.

Hemodynamic monitoring in liver transplantation

Zhuravel S.V., Kuznetsova N.K., Statsura V.E., Gavrilov P.V., Goncharova I.I.

Sklifosovsky Research Institute for Emergency Medicine, Moscow, Russia

UDK 581.143.4

DOI: 10.53652/2782-1730-2022-3-2-36-43

Abstract. Hemodynamic monitoring is an important part of the anesthetic management in liver transplantation. Currently, there is no unified algorithm for the assessment of the cardiovascular system parameters. The article describes the criteria for the presence or absence of the necessity of using routine or additional invasive monitoring methods.

Keywords: hemodynamic monitoring, liver transplantation, invasive monitoring.

Introduction. Liver transplantation (LT) is a surgical intervention, which may be accompanied by significant hemodynamic instability due to blood loss, sudden changes in preload, myocardial dysfunction, reduced response of cardiovascular system (CVS) to cardiotonic drugs. Hypotension and arterial pressure (AP) variability occurring in the perioperative period entail increased mortality within 30 days after surgery, transplant dysfunction, and acute renal failure [1]. Advanced anesthesiological hemodynamic monitoring allows diagnosing the problem in real time and solving it with targeted therapy [2].

Until now, there is no unified methodology of routine monitoring of CVS parameters in orthotopic LT that can be considered as suitable for all clinical situations [3]. The question about to which patient, in what volume and what hemodynamic monitoring should be used for LT is of current concern.

History. The first experimental liver transplantations were performed in the late 1950s and early 1960s by surgeon Thomas E. Starzl. On March 1, 1963, he performed the world's first liver transplantation. The patient was a 3-year-old boy with biliary atresia who died because of hemostasis disorders and massive bleeding [4-8]. During this period, AP was measured using a sphyngomanometer, and electrical activity of the heart was assessed by electrocardiogram (ECG) [9].

Since 1980s the mandatory CVS monitoring included AP measurement (using arterial catheter), heart rate (HR), ECG and control of central hemodynamic parameters using Swan-Ganz catheter. These classic anesthesiology parameters are still used [10, 11]. At the present stage new technologies and less invasive ways of hemodynamic parameters measurement are being developed, the effectiveness of which in morbidity and mortality reduction is still a subject of discussion [3].

Currently, the survival rate of patients within the first year after LT is more than 90% [12-14].

Unquestionably, optimization of anesthesiological monitoring during LT is of great significance for the improvement of the outcomes for this surgery.

Pathophysiology. Patients with liver cirrhosis (LC) have a hyperdynamic type of circulation. Decrease of venous and arterial vascular tone leads to decrease of postload, as a result of compensatory reactions the cardiac output (CO) increases. This fact often hides left ventricular (LV) function insufficiency, which is characterized by decreased contractility. Also in patients with LC the chronotropic response to stress is impaired, the phase of diastolic ventricular relaxation is reduced and the QT interval is prolonged. Surgical manipulations can cause even more reduction of venous return and preload, which are aggravated by a vasoconstrictive reaction, vasodilatation of the venous bed and coagulopathy [16-18].

Orthotopic liver transplantation includes 3 main stages: access and hepatectomy, anhepatic stage, reperfusion [19].

In the first stage the surgeon mobilizes the liver of the recipient, interrupts the blood supply to the liver by the inferior vena cava, as well as the arterial and portal blood flow. Blood loss, hypovolemia and retraction of the inferior vena cava significantly reduce venous return. In the ahepatic stage (second stage) with complete clamping of the portal vien and inferior vena cava CO can decrease by up to 50%. This decrease can be minimized by partial clamping of inferior vena cava, formation of temporary portocaval shunt [20]. In this regard, preload reduction is the main hemodynamic feature of this phase. The third phase begins with reperfusion and continues until the end of surgical intervention. In this phase, postreperfusion syndrome can develop. It is characterized by the inflow of cold fluid from the graft into the systemic bloodstream in the inferior vena cava and the right atrium. This fluid is rich in proinflammatory and vasodilatory mediators and potassium, which, reaching the great circle of circulation, cause even greater decrease of vascular tone and aggravate right ventricular (RV) overload [21-23].

Timely diagnosis of these intraoperative challenges is possible due to advanced hemodynamic monitoring during liver transplantation.

Methods of hemodynamic monitoring. ***Arterial catheter: radial or femoral access?*** Researchers have different opinions on this question. It is believed that femoral access is preferable because it is closer to the aorta and the measured value corresponds to the central arterial pressure (CAD). The discrepancy between CAD and mean arterial pressure (MAP) measured through the radial artery (RA) was only in case of therapy with high doses of vasopressor drugs [24].

Hypotension and arterial pressure (AP) variability occurring in the perioperative period entail increased mortality within 30 days after surgery, transplant dysfunction, and acute renal failure [1]. Advanced anesthesiological hemodynamic monitoring allows diagnosing the problem in real time and solving it with targeted therapy

There is an evidence that MAP measured in femoral artery is a more accurate indicator compared to the data when it is measured in the RA [25]. According to other sources, no difference between the MAP measured in the LA and the MAP measured in the femoral artery was found, or only systolic AP differences were found during reperfusion and only in cases of high-dose vasopressors [26].

Patients with LC tend to suffer from hemostasis disorders, in which arterial catheter placement may result in bleeding and hematoma development. An arterial catheter inserted into the RA is considered to be no less informative, but safer in terms of complications than an arterial catheter inserted into the femoral artery.

The Swan-Ganz catheter. It allows assessing changes in CO, central venous pressure (CVP), pulmonary artery pressure (PAP), pulmonary capillary occlusion pressure (PCOP) and mixed venous blood oxygen saturation (ScVO2). According to the classical Frank-Starling law, which relates myocardial fiber length to the force developed by the ventricle to eject blood, the end-diastolic volume, which determines stretch, is proportional to the end-diastolic pressure in the right and left ventricles. This pressure can be estimated by CVP for RV and by PCOP for LV [27].

Unfortunately, both CVD and PCOP have shown little prognostic value in the management of hemodynamics in patients with LT [28]. The reason why Swan-Ganz catheter is still used in LT is control of PAP, PCOP, as well as CO measurement by thermodilution. An average PAP above 50 mmHg is considered a contraindication for surgery because of the high mortality rate (>70%). Treatment of

elevated PAP during LT in mild to moderate pulmonary hypertension includes the use of veno-venous shunt during the ahepatic phase, phosphodiesterase-5 inhibitors, endothelin receptor antagonists and prostacyclins, as well as requires continuous monitoring of PCOP [29-31].

Minimally invasive monitoring system Flotrac/Vigileo. The interest of anesthesiologists-resuscitators to less invasive methods of hemodynamic monitoring in LT has led to the emergence of many technologies, one of which was the application of Flotrac/Vigileo device, which allows to measure stroke volume (SV) and circulating blood volume (CBV) based on the analysis of pulse wave recorded from the peripheral arteries (radial or femoral) depending on each stroke. According to these indicators, we can judge the degree of hydration of the patient's body and the response of the CVS to the infusion therapy [32].

There is no difference in measurements of variation of hemodynamic indices obtained from either radial or femoral catheter. However, unfortunately, research results have not proved diagnostic advantage in LT, especially in patients with terminal severity LC (Child-Pugh C), as well as in patients with hyperdynamic type of circulation (CB>8 l/min). Flotrac/Vigileo cannot replace the examination of hemodynamic parameters using Swan-Ganz catheter [33].

Transesophageal echocardiography. According to a number of authors, transesophageal echocardiography (TEE) during LT in 72.9% of cases helps to quickly differentiate the etiology of hemodynamic disorders and determine the treatment tactics [34].

The advantages of TEE during LT allow:

- to identify the causes of hemodynamic instability: hypovolemia, RV dysfunction, LV dysfunction, intracardiac thrombosis, pulmonary embolism or thrombosis [35];
- to detect the presence of hepatic vein of the graft or inferior vena cava obstruction during the extrahepatic phase [36];
- to control the effectiveness of pharmacotherapy in the treatment of refractory intraoperative hypotension [37].

The TEE also has limitations:

- lack of special training of anesthesiologists;
- insufficient time to analyze the data obtained from all sources of monitoring and making decisions regarding further therapy in conditions of acute hemodynamic instability;
- subjectivity of the method;
- TEE cannot replace Swan-Ganz catheter (in patients who need direct and accurate measurements of pressure in the pulmonary artery) and eliminate its well-described complications [38].

Patients with LC are at high risk of bleeding from esophageal varices (EV), so the risk/benefit ratio of TEE makes it unreasonable, which means that its routine application remains questionable [39].

Based on the aforementioned, TEE should be considered as an adjunct to other hemodynamic monitoring tools and should be used in situations where additional information would facilitate diagnosis and/or change tactics: patients at high risk of cardiovascular complications, with a history of poor cardiovascular outcomes. TEE should not be used in patients at high risk of EV bleeding. The method should only be used by trained medical personnel.

Invasive monitoring system PiCCO. PiCCO is an invasive monitoring method that integrates a wide range of hemodynamic data through transcardiopulmonary thermodilution measurement and pulse contour analysis. It is considered a less invasive method of CO monitoring than the Swan-Ganz catheter. The necessity of central vein and artery catheterization makes its parameters more informative than those of minimally or noninvasive devices [40, 41].

Using PiCCO it is possible to measure: Transpulmonary cardiac output (CO); PiCCO — continuous CO pulse index; EVLW — extravascular water in lungs; GEDV — global end-diastolic volume; ITBV — intrathoracic blood volume; CFI — cardiac function index (CI); PVPI — pulmonary vascular permeability index; LVCI — LV contractility index; GEF — global ejection fraction [42].

Continuous analysis of the above-described parameters showed better correlation with cardiac performance compared to other devices in critical patients. Also PiCCO more accurately reflects LV filling in patients who underwent LT [43]. A patient with suspected hypovolemia will have increased CO level in response to fluid infusion, which allows the clinician to modify infusion therapy and avoid hypo- or hyperhydration. This aspect is very important in LT in the condition of ongoing bleeding [44-46].

Although the value of practical application of PiCCO is quite high, this method requires additional central venous access and femoral artery catheterization.

Experience of the Scientific Research Institute for Emergency Medicine (SRI EM) named after N.V. Sklifosovsky. From 2000 to the present time, 950 TP operations have been performed in the SRI EM named after N.V. Sklifosovsky. During this period the anesthesiological monitoring in TP has undergone changes, with the experience came the understanding of the necessity of routine use of one or another monitoring parameter.

From 2000 till 2010 in addition to standard hemodynamic monitoring of indirect arterial pressure (IAP), ECG, heart rate in 168 cases the Swan-Hantz catheter was routinely installed and the parameters of CVP, PAP were monitored in continuous mode. Cardiac output was measured by thermodilution method, as well as PCOP, CI and total peripheral vascular resistance (TPVR) parameters were assessed.

From the end of 2010 to 2016 in 246 cases extended monitoring was performed using Vigileo monitor (Edwards Lifesciences). Standard parameters were extended by continuous measurement of CO, CI, SV, the ratio of stroke volume variation to stroke volume (SVV/SV) and central venous blood oxygen saturation (ScVO2).

Since 2017, additional invasive hemodynamic monitoring in patients with MELD<30 is limited to direct measurement of CVP and AP.

We use continuous measurement of CO and SvO2 of mixed venous blood (Vigileo monitor) during LT in a patient with fulminant course of hepatic failure, with MELD>30, hepatopulmonary syndrome, as well as with a history of a previous infarction.

It should be noted that decompensated diseases of the cardiovascular and respiratory systems are contraindications for LT.

The main problem of invasive monitoring with Swan-Ganz catheter is mandatory formation of an additional vascular access (in addition to the basic one for infusion). For pulmonary artery catheterization we punctured the right internal jugular vein.

At the same time, the Vigileo monitor is a system for monitoring CO by AP indicator (APCO technology) and suggests the possibility of RA catheterization, without the need for additional central venous access.

Currently, we successfully use one of the ports of a triple-lumen high-flow catheter inserted either into the subclavian or internal jugular vein to measure CVP, which also avoids the formation of another central venous access, especially in patients with severe initial hypocoagulation disorders.

Over the last 15 years, the survival rates of patients after LT have significantly increased, and this fact allows to state with full confidence that optimization of additional hemodynamic monitoring plays a significant role in the success of these surgical interventions. Individual approach to each patient taking into account the severity of his initial condition and the presence of concomitant pathology makes it possible to clearly determine the need for the use of additional monitoring methods (Swan-Hans catheter, Vigileo monitor) or the routine use of invasive monitoring of CVP and AP before the surgery.

Conclusion. None of the available hemodynamic monitors or diagnostic devices (including TEE) alone improves outcomes. The information obtained from various sources should be interpreted followed by appropriate clinical actions. Undoubtedly, invasive hemodynamic monitoring is irreplaceable in LP. However, the decision on additional monitoring, on the specific parameters required for the control should be individual for each patient.

If prolonged surgical intervention in a patient with severe hemostasis disorders is expected, an arterial catheter should be placed in the RA. It allows to avoid hemorrhagic complications in the peri- and early postoperative period provided adequate monitoring.

If the patient has mild to moderate pulmonary hypertension, the Swan-Ganz catheter is likely to be required to monitor parameters to assess the possible development of acute pulmonary hypertension.

In the presence of cardiac pathology, it makes sense to add TEE to additional monitoring. However, it should not be used in patients at high risk of EV bleeding.

None of the available hemodynamic monitors or diagnostic devices (including TEE) alone improves outcomes. The information obtained from various sources should be interpreted followed by appropriate clinical actions. Undoubtedly, invasive hemodynamic monitoring is irreplaceable in LP. However, the decision on additional monitoring, on the specific parameters required for the control should be individual for each patient

References

1. Mizota T, Hamada M, Matsukawa S, Seo H, Tanaka T, Segawa H. Relationship Between Intraoperative Hypotension and Acute Kidney Injury After Living Donor Liver Transplantation: A Retrospective Analysis. *J Cardiothorac Vasc Anesth*. 2017; 31(2):582–589. https://doi.org/10.1053/j.jvca.2016.12.002
2. Davydov DV, Untu FI, Rudenko MI. Monitoring central'noj i perifericheskoj gemodinamiki pri endoprotezirovaniitazobedrennyh sustavov v usloviyah razlichnyh metodov anestezii. Vysokotekhnologichnaya specializirovannaya medicinskaya pomoshch': Abstracts of the Scientific and Practical Conference. Moscow: N.N. Burdenko GGVG; 2006. P. 276–277. (In Russ.).
3. Della Rocca G, Chiarandini P. Hemodynamic Monitoring During Liver Transplantation. *Int Anesthesiol Clin*. 2017; 55(2):121–134. https://doi.org/10.1097/AIA.0000000000000144

4. Starzl TE, Kaupp HA Jr, Brock DR, Lazarus RE, Johnson RV. Reconstructive problems in canine liver homotransplantation with special reference to the postoperative role of hepatic venous flow. *Surg Gynecol Obstet*. 1960; 111:733–43. PMID: 18979655
5. Kaupp HA Jr, Starzl TE. The use of an external bypass during experimental total hepatectomy. *Surgery*. 1960; 48:330–1. PMID: 14404925
6. Starzl TE, Marchioro TL, Vonkaulla KN, Hermann G, Brittain RS, Waddell WR. Homotransplantation of the liver in humans. *Surg Gynecol Obstet*. 1963; 117:659–76. PMID: 14100514
7. Starzl T, Groth CG, Brettschneider L, Penn I, Fulginiti VA, Moon JB, et al. Orthotopic homotransplantation of the human liver. *Ann Surg*. 1968; 168(3):392–415. https://doi.org/10.1097/00000658-196809000-00009
8. Starzl TE, Putnam CW. *Experience in hepatic transplantation*. Philadelphia: WB Saunders Company; 1969. https://doi.org/10.7326/0003-4819-72-2-295
9. Farman JV. Anaesthesia in the presence of liver disease and for hepatic transplantation. *Br J Anaesth*. 1972; 44(9):946–952. https://doi.org/10.1093/bja/44.9.946
10. Waterman PM. Anaesthesia for liver transplantation — a model for the anaesthetic management of end-stage hepatic failure. *Can Anaesth Soc J*. 1983; 30(3Pt2):S34–38. https://doi.org/10.1007/BF03009976
11. Shiao J, Haosheng B, Zicheng M, Chongrong G. Anaesthesia in orthotopic liver transplantation. Report of 8 cases. *Anaesthesist*. 1981; 30(9):447–51. PMID: 7025697
12. Pruinelli L, Monsen KA, Gross CR, Radosevich DM, Simon GJ, Westra BL. Predictors of Liver Transplant Patient Survival. *Prog Transplant*. 2017; 27(1):98–106. https://doi.org/10.1177/1526924816680099
13. Olisov OD, Novruzbekov MS, Galankina IE, Zimina LN, Gulyaev VA, Donova LV, et al. Liver Transplantation in the Treatment of Unresectable Hepatocellular Carcinoma in the Absence of Liver Cirrhosis. *Russian Journal of Gastroenterology, Hepatology, Coloproctology*. 2018; 28(4):76–83 (In Russ). https://doi.org/22416/1382-4376-2018-28-4-76-83
14. Mateo R, Cho Y, Singh G, Stapfer M, Donovan J, Kahn J, et al. Risk factors for graft survival after liver transplantation from donation after cardiac death donors: an analysis of OPTN/UNOS data. *Am J Transplant*. 2006; 6(4):791–6. https://doi.org/10.1111/j.1600-6143.2006.01243.x
15. Ruiz-del-Árbol L, Serradilla R. Cirrhotic cardiomyopathy. *World J Gastroenterol*. 2015; 21(41):11502–21. https://doi.org/10.3748/wjg.v21.i41.11502
16. Yoon KT, Liu H, Lee SS. Cirrhotic Cardiomyopathy. *Curr Gastroenterol Rep*. 2020; 22(9):45. https://doi.org/10.1007/s11894-020-00783-1
17. Elleuch N, Mrabet S, Ben Slama A, Jaziri H, Hammami A, Brahim A, et al. Cirrhotic cardiomyopathy. *Tunis Med*. 2020; 98(3):206–210. PMID: 32395813
18. Szewc UZ, Tronina O, Wyzgal J. Assessment of Hemodynamic Parameters in Recipients of a Liver Transplant. *Transplant Proc*. 2020; 52(8):2459–2462. https://doi.org/10.1016/j.transproceed.2020.03.037
19. Hackl C, Schmidt KM, Süsal C, Döhler B, Zidek M, Schlitt HJ. Split liver transplantation: Current developments. *World J Gastroenterol*. 2018; 24(47):5312–5321. https://doi.org/10.3748/wjg.v24.i47.5312
20. Chen M, Ju W, Lin X, Chen Y, Zhao Q, Guo Z, et al. An Alternative Surgical Technique of Native Hepatectomy in Liver Transplantation. *Ann Transplant*. 2021; 26:e929259. https://doi.org/10.12659/AOT.929259
21. Carvalho MVH, Kroll PC, Kroll RTM, Carvaho VN. Cirrhotic cardiomyopathy: the liver affects the heart. *Braz J Med Biol Res*. 2019; 52(2):e7809. https://doi.org/10.1590/1414-431X20187809
22. Wray CL. Liver Transplantation in Patients with Cardiac Disease. *Semin Cardiothorac Vasc Anesth*. 2018; 22(2):111–121. https://doi.org/10.1177/1089253217736050
23. Bezinover D, Mukhtar A, Wagener G, Wray C, Blasi A, Kronish K, et al. Hemodynamic Instability During Liver Transplantation in Patients with End-stage Liver Disease: A Consensus Document from ILTS, LICAGE, and SATA. *Transplantation*. 2021; 105(10):2184–2200. https://doi.org/10.1097/TP.0000000000003642
24. Stern DH, Gerson JI, Allen FB, Parker FB. Can we trust the direct radial artery pressure immediately following cardiopulmonary bypass? *Anesthesiology*. 1985; 62(5):557–61. https://doi.org/10.1097/00000542-198505000-00002
25. Катин М.Л., Дзядзько А.М., Гурова М.Ю., Руммо О.О. Мониторинг артериального давления при трансплантации печени: способ измерения имеет значение. *Трансплантология*. 2019; 11(2):116–127. [Katin ML, Dzyadz`ko AM, Gurova MYu, Rummo OO. Blood pressure monitoring during liver transplantation: the method of measurement does matter. *Transplantology. The Russian Journal of Transplantation*. 2019; 11(2):116–127 (In Russ)]. https://doi.org/10.23873/2074-0506-2019-11-2-116-127
26. Arnal D, Garutti I, Perez-Peña J, Olmedilla L, Tzenkov IG. Radial to femoral arterial blood pressure differences during liver transplantation. *Anaesthesia*. 2005; 60(8):766–771. https://doi.org/10.1111/j.1365-2044.2005.04257.x
27. Brezeanu LN, Brezeanu RC, Diculescu M, Droc G. Anaesthesia for Liver Transplantation: An Update. *J Crit Care Med (Targu Mures)*. 2020; 6(2):91–100. https://doi.org/10.2478/jccm-2020-0011
28. Isidoro Duarte T, Amaral M, Pires C, Casimiro J, Germano N. Hemodynamic monitoring for liver transplantation: Agreement between invasive and non-invasive devices? *Med Intensiva (Engl Ed)*. 2021 Aug; 19:S0210-5691(21)00171-6.https://doi.org/10.1016/j.medin.2021.06.005
29. Villa AM, Pagano M, Fallabrino G, Piccioni F, Manzi RC, Codazzi D, et al. Comparison Between Swan-Ganz Catheter and Minimally Invasive Hemodynamic Monitoring During Liver Transplantation: Report of a Monocentric Case Series. *Transplant Proc*. 2019; 51(9):2943–2947. https://doi.org/10.1016/j.transproceed.2019.04.094
30. Ramsay MA, Simpson BR, Nguyen AT, Ramsay KJ, East C, Klintmalm GB. Severe pulmonary hypertension in liver transplant candidates. *Liver Transpl Surg*. 1997; 3(5):494–500. https://doi.org/10.1002/lt.500030503
31. Krowka MJ, Mandell MS, Ramsay MA, Kawut SM, Fallon MB, Manzarbeitia C, et al. Hepatopulmonary syndrome and portopulmonary hypertension: a report of the multicenter liver transplant database. *Liver Transpl*. 2004; 10(2):174–182. https://doi.org/10.1002/lt.20016
32. De Backer D, Marx G, Tan A, Junker C, Van Nuffelen M, Hüter L, et al. Arterial pressure-based cardiac output monitoring: a multicenter validation of the third-generation software in septic patients. *Intensive Care Med*. 2011; 37(2):233–240. https://doi.org/10.1007/s00134-010-2098-8
33. Lee M, Weinberg L, Pearce B, Scurrah N, Story DA, Pillai P, et al. Agreement in hemodynamic monitoring during orthotopic liver transplantation: a comparison of FloTrac/Vigileo at two monitoring sites with pulmonary artery catheter thermodilution. *J Clin Monit Comput*. 2017; 31(2):343–351. https://doi.org/10.1007/s10877-016-9840-x
34. Staudt GE, Shelton K. Development of a Rescue Echocardiography Protocol for Noncardiac Surgery Patients. *Anesth Analg*. 2019; 129(2):e37–e40. https://doi.org/10.1213/ANE.0000000000003569
35. Vanneman MW, Dalia AA, Crowley JC, Luchette KR, Chitilian HV, Shelton KT. A Focused Transesophageal Echocardiography Protocol for Intraoperative Management During Orthotopic Liver Transplantation. *J Cardiothorac Vasc Anesth*. 2020; 34(7):1824–1832. https://doi.org/10.1053/j.jvca.2020.01.028
36. Braun HJ, Pulcrano ME, Weber DJ, Padilla BE, Ascher NL. The utility of ECMO after liver transplantation: Experience at a high-volume transplant center and review of the literature. *Transplantation*.2019; 103(8):1568–1573. https://doi.org/10.1097/TP.0000000000002716
37. Gold AK, Patel PA, Lane-Fall M, Gutsche JT, Lauter D, Zhou E, et al. Cardiovascular collapse during liver transplantation-echocardiographic-guided hemodynamic rescue and perioperative management. *J Cardiothorac Vasc Anesth*. 2018; 32(5):2409–2416. https://doi.org/10.1053/j.jvca.2018.01.050
38. Cywinski JB, Maheshwari K. Con: Transesophageal Echocardiography Is Not Recommended as a Routine Monitor for Patients Undergoing Liver Transplantation. J Cardiothorac Vasc Anesth. 2017; 31(6):2287–2289. https://doi.org/10.1053/j.jvca.2016.11.037
39. Elsayed H, Page R, Agarwal S, Chalmers J. Oesophageal perforation complicating intraoperative transoesophageal echocardiography: Suspicion can save lives. *Interact Cardiovasc Thorac Surg*. 2010; 11(3):380–2. https://doi.org/10.1510/icvts.2010.233338
40. Litton E, Morgan M. The PiCCO monitor: a review. *Anaesth Intensive Care*. 2012; 40(3):393–409. https://doi.org/10.1177/0310057X1204000304
41. Oren-Grinberg A. The PiCCO Monitor. *Int Anesthesiol Clin*. 2010; 48(1):57–85. https://doi.org/10.1097/AIA.0b013e3181c3dc11
42. Martín Vivas A, Saboya Sánchez S, Patiño Rodríguez M, Silva Obregón JA, Gómez Rosado S, Blanco García JJ. Monitorización hemodinámica: sistema PiCCO [Hemodynamic monitoring: PiCCO system]. *Enferm Intensiva*. 2008; 19(3):132–140. https://doi.org/10.1016/s1130-2399(08)72755-x
43. Costa MG, Chiarandini P, Della Rocca G. Hemodynamics during liver transplantation. *Transplant Proc*. 2007; 39(6):1871–1873. https://doi.org/10.1016/j.transproceed.2007.05.002
44. Wyler Von Ballmoos M, Takala J, Roeck M, Porta F, Tueller D, Ganter CC, et al. Pulse-pressure variation and hemodynamic response in patients with elevated pulmonary artery pressure: a clinical study. *Crit Care*. 2010; 14(3):R111. https://doi.org/10.1186/cc9060
45. Della Rocca G, Costa MG, Coccia C, Pompei L, Pietropaoli P. Preload and haemodynamic assessment during liver transplantation: a comparison between the pulmonary artery catheter and transpulmonary indicator dilution techniques. *Eur J Anaesthesiol*. 2002; 19(12):868–75. https://doi.org/10.1017/s0265021502001394
46. Costa MG, Girardi L, Pompei L, Chiarandini P, De Flaviis A, Lugano M, et al. Perioperative intra- and extravascular volume in liver transplant recipients. *Transplant Proc*. 2011; 43(4):1098–102. https://doi.org/10.1016/j.transproceed.2011.03.022.

Information about the authors:

Sergej V. Zhuravel — MD, DSc, Head of the Scientific Department of Anesthesiology and Resuscitation in Sklifosovsky Research Institute for Emergency Medicine, Moscow, Russia — **responsible for contacts**, **ZhuravelSV@sklif.mos.ru**, ORCID: 0000-0002-9992-9260

Natal'ya K. Kuznecova — MD, PhD, Leading Researcher, Department of Anesthesiology and Resuscitation in Sklifosovsky Research Institute for Emergency Medicine, Moscow, Russia.

Viktoriya E. Stacura — Researcher, Department of Anesthesiology and Resuscitation in Sklifosovsky Research Institute for Emergency Medicine, Moscow, Russia.

Pavel V. Gavrilov — Junior Researcher, Department of Anesthesiology and Resuscitation in Sklifosovsky Research Institute for Emergency Medicine, Moscow, Russia.

Irina I. Goncharova — MD, PhD, Senior Research Fellow, Department of Anesthesiology and Resuscitation in Sklifosovsky Research Institute for Emergency Medicine, Moscow, Russia.

The authors declare no conflicts of interest.
The study was not sponsored.
Received 22.02.2022.

Extracorporeal detoxification in intensive care of metabolic acidosis in cancer patients

UDK 616.152.112
DOI: 10.53652/2782-1730-2022-3-2-44-47

Gromova E.G.

Federal State Budgetary Institution «N.N. Blokhin National Medical Research Center of Oncology» of the Ministry of Health of the Russian Federation (N.N. Blokhin NMRCO), Moscow, Russia

Abstract. Metabolic acidosis is a satellite and a consequence of a number of damaging factors; it belongs to the category of critical pathological conditions, associated with high mortality, and requires appropriate intensive therapy. In cancer patients, the risk of decompensated homeostasis disorders is significantly higher compared to the general population of patients, which reduces the possibility of antitumor treatment and worsens the prognosis. Timely application of extracorporeal detoxification allows to avoid fatal complications and continue antitumor treatment.

Keywords: metabolic acidosis, extracorporeal detoxification, cancer.

Introduction. Progressive tissue hypoxia of various etiology activates anaerobic glycolysis with disruption of pyruvic acid synthesis and lactic acid decomposition with pyruvate dehydrogenase, followed by excess lactic acid formation. Lactate acidosis refers to a variant of metabolic acidosis, characterized by an increase in anion gap and a decrease in blood pH ≤7.35 with a simultaneous increase in serum lactate concentration over 5 mmol/l. Lactic acid is a normal end product of glucose metabolism through the anaerobic glycolysis pathway. With adequate oxygenation and nutrition, cells receive the necessary energy from the end product of glycolysis, pyruvate, which is converted to acetyl coenzyme A by pyruvate dehydrogenase, with the participation of thiamine, a cofactor of this reaction.

Acetyl-Coenzyme A is incorporated into the tricarboxylic acid cycle via the mitochondria of the cells. Increased energy expenditure and catabolism lead to rapid depletion of glycogen as the main energy source. Reduced insulin secretion and activity under shock conditions, production of counterinsulin hormones, insulin-like growth factors aggravate glucose metabolism disorders, resulting in increased lipolysis and ketogenesis, accumulation of free fatty acids and progression of acidosis due to incomplete oxidation of ketone bodies in the liver [1].

Two principal types of lactate acidosis are distinguished: type "A", caused by hypoxia and tissue hypoperfusion, and type "B", associated with comorbid pathology, trauma, the presence of malignant tumors, drug and other toxicity, as well as with congenital abnormalities of mitochondrial processes [2].

In oncology, the development of lactate acidosis due to malignancy itself was first described in 1963 [3].

More often it is associated with oncohematological diseases, primarily acute leukemia and lymphoma [4, 5], and is known as "Warburg effect" [6].

The Warburg effect is the tendency of malignant cells to produce energy preferentially by immediate glycolysis and pyruvate oxidation in mitochondria with the involvement of oxygen, whereas very active glycolysis with subsequent formation of lactic acid, even under conditions of normoxia and hyperoxia and tissue normoxygenation. Processes of oxygen-dependent oxidative pathway are forced to slow down, largely due to the outrunning growth of the tumor compared to neoangiogenesis and development of oxygen and nutritive deficiency, which can lead to 200-fold increase of glycolysis level in the cells of fast growing malignant tumor in comparison with the cells of normal tissues. Individual cases of severe lactate acidosis in patients with solid tumors have been described [7, 8], including anti-tumor treatment and thiamine deficiency [9].

In oncology patients, to the concomitant or acutely developed disorders of ventilation-perfusion relations in the lungs and intravascular oxygen transport are added:

- presence of a malignant neoplasm as such;
- drug antitumor treatment, including methotrexate;
- hyperproduction of lactate due to thiamine and riboflavin deficiency;
- decreased hepatic clearance of lactate;
- embolization of the microvascular bed by malignant cells;
- anemia due to antitumor drug treatment with hematologic toxicity, suppression of bone marrow hematopoiesis in sepsis, impaired production of endogenous erythropoietin in the development of acute renal failure;
- susceptibility of cancer patients to septic complications with impaired tissue perfusion and predominance of anaerobic type of metabolism.

All these factors aggravate hypoxia and the risk of decompensated lactate acidosis, characterized by mortality over 50% in the general population and over 80% in cancer patients [10].

Increasing lactacidemia and bicarbonate buffer deficiency leads to bradycardia and decreased cardiac output and minute volume, blockade of adrenergic receptors in the cardiovascular system and paralysis of vasoconstrictor effect of catecholamines, which complicates the manifestation of shock and promotes the development of decompensated organ/polyorgan failure. Disorders of tissue and vascular permeability typical of intensive care patients, intensifying in conditions of cytopenia, accompanied by entry of excess lactate through the blood-brain barrier, with the development of neurotoxic damage.

Lactate acidosis has long been among the non-renal indications for renal replacement therapy (RRT) [11, 12]. Regardless of the type of lactate acidosis and modality of RRT, its use along with conservative methods of treatment is accompanied by a significantly higher survival rate, especially when high lactate clearance is achieved in the first 6 hours after the beginning of intensive therapy [13]. There have been no valid studies on the use of RRT methods in intensive care of decompensated lactate acidosis in patients with solid tumors in oncopediatrics, but there are single reports on successful combined intensive care [14].

Clinical case. Patient T., 11 years old, was treated at the National Medical Research Center of Oncology named after N.N. Blokhin of the Ministry of Health of the Russian Federation with the diagnosis: osteosarcoma of the left fibula.

On the 15th day after the first course of polychemotherapy (PCT) including cisplatin and doxorubicin, grade III leukopenia (decrease in leukocyte count to <2×109/l) and grade II thrombocytopenia (decrease in platelet count to <50×109/l) developed. After the blood values were restored, the 2nd course of PCT with cisplatin, doxorubicin, and high-dose methotrexate was performed. On the 14th day after the 2nd course hematologic toxicity of IV degree developed (decrease in leukocyte count <1×109/l), significant electrolyte disorders: hyponatremia - 127.1 mmol/l, hypokalemia - 2.77 mmol/l, hypochloremia - 93.1 mmol/l, hypocalcemia — 1.67 mmol/l, thrombohemorrhagic syndrome. Left-sided lower lobe pneumonia was diagnosed on the 45th day after the beginning of the 2nd course of PCT. Despite intensive therapy, the child's condition worsened: consciousness - deep sopor. Increasing tachypnea up to 30 per minute and decrease of SpO2 saturation to 81-83% were noted. The patient was put on artificial lung ventilation in the preexpiratory mode: PEEP - 9 cm H2O; PC — 17 cm H2O; FiO_2 — 60%; SpO_2 — 97-100%; vasopressor support with noradrenalin at a dose of 0.25 μg/kg/min was started. Central venous pressure was at 26-28 cm H2O. Pancytopenia persisted: white blood cell count was 1.6×109/l, platelets 27×109/l, hemoglobin 67 g/l. Against the background of thrombocytopenia (63×109/l), a profuse hemorrhagic discharge was noted through the nasogastric tube. Abdomen was swollen, painless on palpation, peristalsis was uncertain; there was no voluntary stool for 7 days. Oligoanuria, anasarca. Increasing azotemia (creatinine — 162 mmol/l, urea — 23 mmol/l), decompensated and resistant to conservative therapy lactate acidosis (lactate — 26 mmol/l; VE — 20 mmol/l; pH — 7.15) were noted. Presepsin level in blood was 2330 pg/ml.

Considering the extremely severe condition of the patient, caused by sepsis, lactate acidosis, anuria, despite the high risk of hemorrhagic, thrombotic and hemodynamic disorders, it was decided to use RRT according to vital indications. Hemodiafiltration was started via a perfusion catheter in the right femoral vein

A wide range of complications, including decompensated lactate acidosis during aggressive antitumor therapy requires further research and development of algorithms of combined intensive therapy for cancer patients with the inclusion of extracorporeal hemocorrection methods

on a Multifiltrat device using KIT 8 (av 1000 filter) and substitute solutions with potassium concentration of 4 mmol/l. Renal replacement therapy was performed at a blood flow rate of 260 ml/min, dialysate and substitute delivery rates of 2,800 ml/h; controlled hypocoagulation with unfractionated heparin with consideration of thrombocytopenia and activated partial thromboplastin time monitoring was 50-100 units/h. Tolerability of RRT was assessed as satisfactory. The duration of the procedure was 21 hours with a total volume of ultrafiltration of 5600 ml, finished due to the need for administration of filtering medications, including antibacterials. By the end of hemodiafiltration, the patient's condition continued to be extremely severe, but we managed to reduce the dose of norepinephrine to 0.03 μg/kg/min; the lactate level was 6 mmol/L, HL — 2.3 mmol/L, pH — 7.5. Within 1 week, the patient underwent 4 more hemodiafiltration procedures, each lasting 4 to 6 h. Hemodynamic and subjective tolerance of extracorporeal detoxification was satisfactory. From the 3rd day there was a progressive recovery of the water-excretory function of the kidneys. Due to a decrease in thrombocyte level to 21 ths/μl, RRT was performed without controlled hypocoagulation. Parallel antibacterial, infusion-transfusion therapy, parenteral nutrition were carried out.

During the next 14 days of treatment, the patient's condition progressively improved: symptoms of multiple organ failure regressed; consciousness recovered; hemodynamic, respiratory and laboratory parameters stabilized; patient was switched to independent breathing; vasopressor support was cancelled; procalcitonin, preseptin and C-reactive protein levels were normalized.

Subsequently, the patient underwent surgical intervention resection of the fibula. The postoperative period was smooth. The patient was discharged for further rehabilitation treatment.

Considering the development of severe sepsis in a patient with multiple organ failure, anuria, decompensated and resistant to conservative therapy lactate acidosis and marked hemodynamic instability based on the overall effectiveness and safety profiles, prolonged hemodiafiltration was the method of choice for RRT.

Conclusion. A wide range of complications, including decompensated lactate acidosis during aggressive antitumor therapy requires further research and development of algorithms of combined intensive therapy for cancer patients with the inclusion of extracorporeal hemocorrection methods.

References

1. Cherniy VI, Shlapak IP, Georgiyants MA, Tyumentseva SG, Kugler SE, Prokopenko BB. Etiology, pathogenesis and intensive care of metabolic acidosis. *Meditsina neotlozhnykh sostoyaniy*. 2016; (6):153–166. (In Russ.). https://doi.org/10.22141/2224-0586.6.77.2016.82183
2. Skvortsov VV, Skvortsova EM, Bangarov RYu. Lactic acidosis in the practice of a resuscitator. *Messenger of Anesthesiology and Resuscitation*. 2020; 17(3):95–100. (In Russ.). https://doi.org/10.21292/2078-5658-2020-17-3-95-100
3. Field M, Block JB, Rall DP. Lactic acidosis in acute leukemia. *Clin Res*. 1963; 11:193–7.
4. Chan FH, Carl D, Lyckholm LJ. Severe lactic acidosis in a patient with B-cell lymphoma: a case report and review of the literature. *Case Rep Med*. 2009; 2009:534561. https://doi.org/10.1155/2009/534561
5. Osipov I, Mikhaylov E, Ivanov V, Salogub GN, Bessmeltsev SS, Chechetkin AV. Lactic acidosis in patients with hematological malignancies: etiology, pathogenesis and therapy. *Bulletin of Hematology*. 2019; 15(1):6–15. (In Russ.).
6. Warburg O. On the origin of cancer cells. *Science*. 1956; 123(3191):309–14. https://doi.org/10.1126/science.123.3191.309
7. Archer S, Bache-Wiig B. Lactic acidosis B associated with solid tumors. *Minn Med*. 1986; 69(9):511–4. PMID: 3020387
8. de Groot R, Sprenger R, Imholz A, Gerding MN. Type B lactic acidosis in solid malignancies. *Neth J Med*. 2011; 69(3):120–3. PMID:21444939
9. Cho YP, Kim K, Han MS, Jang HJ, Kim JS, Kim YH, et al. Severe lactic acidosis and thiamine deficiency during total parenteral nutrition – case report. *Hepatogastroenterology*. 2004; 51(55):253–5. PMID: 15011878
10. Held-Warmkessel J, Dell DD. Lactic acidosis in patients with cancer. *Clin J Oncol Nurs*. 2014; 18(5):592–4. https://doi.org/10.1188/14.CJON.592-594
11. Schetz M. Non-renal indications for continuous renal replacement therapy. *Kidney Int Suppl*. 1999; (72):S88–94. PMID: 10560814
12. Cerdá J, Tolwani AJ, Warnock DG. Critical care nephrology: management of acid-base disorders with CRRT. *Kidney Int*. 2012; 82(1):9–18. https://doi.org/10.1038/ki.2011.243
13. Nguyen H, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med*. 2004; 32(8):1637–42. https://doi.org/10.1097/01.ccm.0000132904.35713.a7
14. Sotnikov A, Gromova E, Petina O. Successful treatment for decompensated lactic acidosis in a child after high-dose chemotherapy. *Vrach*. 2018; 29(8):44–48. (In Russ.). https://doi.org/10.29296/25877305-2018-08-11

Information about the author:

G. Gromova — MD, ScD, anaesthesiologist, expert in resuscitation, Federal State Budgetary Institution «N.N. Blokhin National Medical Research Center of Oncology» of the Ministry of Health of the Russian Federation (N.N. Blokhin NMRCO), Moscow, Russia — **e_gromova05@mail.ru**, ORCID: 0000-0002-4633-8301

The authors declare no conflicts of interest.
The study was not sponsored.
Received 01.06.2022

Medical Bulletin of the Main Military Clinical Hospital named after N.N. Burdenko

Non transfusion dependent thalassaemia: conventional and novel therapy

UDK 616.155.194.125
DOI: 10.53652/2782-1730-2022-3-2-48-59

Asadov Ch.D.

National Center of Hematology and Transfusiology, Baku, Azerbaijan

Abstract. This literature review attempts to describe modern approaches to the diagnosis and therapy of non transfusion dependent thalassaemia (NTDT). NTDT has a wide clinical spectrum. The clinical polymorphism of the disease is due to genetic heterogeneity. There are three major factors, which are responsible for the clinical manifestations of NTDT: ineffective erythropoiesis, chronic anemia, and iron overload.
Untreated NTDT is the cause of various complications: splenomegaly, gallstones, extramedullary erythropoiesis, kidney stones, lower limbs trophic ulcers, thrombophilia, pulmonary hypertension, endocrine complications, iron overload, bone abnormalities, osteoporosis.
Traditional therapy for NTDT include splenectomy, transfusion therapy, stimulation of fetal hemoglobin (HbF) synthesis, and bone marrow transplantation.
However, due to the limitations and challenges associated with available conventional therapies, novel methods are currently being developed. These include: JAK2 inhibition, hepcidin modulation, TMPRSS6 inhibition, apo-transferrin, HIF2–inhibition, Activin receptor-II trap ligands, ferroportin inhibitors.

Keywords: non transfusion dependent thalassaemia, genetic heterogeneity, clinical polymorphism, transfusion therapy, chelating therapy, modulation of fetal hemoglobin, bone marrow transplantation, gene therapy, novel therapy.

Introduction. Beta-thalassemia (β-thalassemia) is a hereditary anemia caused by mutations in the HBB gene which encodes the β-globin peptide of hemoglobin (Hb), resulting in abnormal erythrocytes with a shortened lifespan [1]. In healthy humans, Hb consists of α- and β-globin chains, which together with the iron-containing heme groups form functional α2β2 heterotetramers in erythrocytes for efficient oxygen delivery to the tissues. The main pathophysiological mechanism in β-thalassemia is a decrease in β-globin chain synthesis, which causes the accumulation of unpaired α-globin aggregates on erythrocyte membranes. The precipitated α-globin aggregates contain heme and iron, which generate reactive oxygen species, resulting in shortened erythrocyte lifespan, anemia, and tissue hypoxia. As a result, erythropoiesis is strongly stimulated in thalassemic patients, resulting in an increased proliferation and decreased differentiation of erythroid precursors in the bone marrow and extramedullary sites, such as the spleen and liver, which is defined as ineffective erythropoiesis [2].

β-thalassemias are widely spread in the Mediterranean, the Middle East and the Indian subcontinent. However, as a result of intense population migration, they are now increasingly common in other countries as well [3]. Thalassemic syndromes are classified as non-transfusion dependent thalassaemia (NTDT) and transfusion dependent thalassemia (TDT), depending on their clinical features and the need for blood transfusion.

Purpose of the review. To describe the etiology, pathogenesis, clinical course of NTDT, and to evaluate the effectiveness of conventional and novel approaches for the treatment of this disease.

Material and methods. A literature search was performed using the PubMed database. The search period was 20 years, from 2003 to 2022. Documents relevant to the topic of the review were selected; secondary citation sources were also analyzed.

The following types of documents were used according to PubMed indexing: Classical Article; Clinical Study; Clinical Trial; Comparative Study; Controlled Clinical Trial; Meta-Analysis; Multicenter Study; Observational Study; Randomized Controlled Trial; Review; Systematic Review.

Genetic heterogeneity of NTDT. The clinical polymorphism of the disease is due to genetic heterogeneity. The majority of patients with NTDT are homozygous or compound heterozygous for β-thalassemia, which means that both β-globin chains are damaged. The milder course of NTDT compared with thalassemia major is caused by the three mechanisms below:

- inheritance of mild β+ mutations;
- increased HbF accompanied by Xmn-enzyme polymorphism on the GA-activator surface;
- simultaneous inheritance of α- and β-thalassemia.

Beta-thalassemia is a hereditary anemia caused by mutations in the HBB gene which encodes the β-globin peptide of hemoglobin, resulting in abnormal erythrocytes with a shortened lifespan

The genotypes leading to NTDT are as follows [4].

Moderate impairment of β-globin chain production:

- moderate homozygous β+-thalassemia;
- compound heterozygosity of severe β0- or β+- or β+- moderate thalassemia;
- the relationship between β0- and " silent " forms of thalassemia;
- homozygosity for "silent" β-thalassemia.

Impairment of β-globin chain imbalance due to combined inheritance of α- and β-thalassemia:

- homozygous or compound-heterozygous β0- or β0+thalassemia with deletion aberrations of α-globin genes;
- homozygous or compound heterozygous β0- or β+thalassemia with non-deletional mutations of α-globin genes;
- moderate β+-thalassemia with increased accumulation of γ-globin chain synthesis;
- homozygous or compound heterozygous β0- or β+-thalassemia with heterocellular hereditary persistence of fetal hemoglobin (HPFH);
- homozygous or compound heterozygous β0- or β+-thalassemia with a specific restriction fragment length polymorphism (RFLP) haplotype of β-globin.

Deletion forms of δβ-thalassemia and HPFH:

- homozygous (δβ)0- or (Aγδβ)0-thalassemia;
- compound heterozygosity of β0- or β+- and (δβ)0- or (Aγδβ)0-thalassemia;
- Hb Lepore homozygosity (in some cases);
- compound heterozygosity for Hb Lepore and β0- or β+-thalassemia (in some cases);
- compound heterozygosity for (δβ)0-, Gγβ+-, or Aγβ+ HPFH and β0- or β+-thalassemia;
- compound heterozygosity for (δβ)0-thalassemia and (δβ)0 HPFH.

Compound heterozygosity for β- or δβ-thalassemia and structural variants of β-globin chains:

- Hb S, C, E/β, or δβ-thalassemia;
- β-thalassemia carriage with a combination of α-globin gene duplications;
- β-globin chain variants with high instability.

Differential diagnosis. The differentiation between TDT and NTDT is particularly important for the planning of necessary therapeutic measures. The main differences between TDT and NTDT are presented in Table 1.

Pathophysiology and complications of NTDT. Three important factors responsible for the clinical manifestation of NTDT: ineffective erythropoiesis, chronic anemia, and iron overload. The severity of the disease depends primarily on the underlying molecular defects. Severe ineffective erythropoiesis leads to bone marrow hyperplasia and extramedullary erythropoiesis, which subsequently causes the distinctive deformity of the skull and facial bones, as well as pathological fractures of long bones [6]. The primary determinant of the development of anemia is ineffective erythropoiesis, whereas the secondary determinants are peripheral hemolysis of mature erythrocytes and a general decrease in Hb synthesis.

In NTDT, in contrast to TDT, where iron overload results from serial blood transfusions, the main cause of iron overload is pathologically increased iron absorption [7, 8].

As shown in Fig. 1, iron absorption and metabolism are stimulated under hypoxia in response to increased erythropoiesis.

Activation of hypoxia-inducible factors (HIFs) increases erythropoietin (EPO) production in the kidneys and decreases hepcidin synthesis in the liver [9, 10, 11]. Iron absorption is regulated by hepcidin, which binds to the iron exporter ferroportin (FPN) and prevents iron escape. Consequently, these two molecules control iron absorption in the duodenum, iron recycling to the reticuloendothelial system, and iron reserves in the liver. Reduced hepcidin levels may also be caused by growth differentiation factor 15 (GDF15), which ultimately leads to increased iron absorption in the duodenum and systemic iron overload [12].

Table 1. Generally accepted criteria for differentiating transfusion dependent thalassemia from non-transfusion dependent thalassemia [5]

Parameters	Characteristic of	
	TDT	NTDT
Clinical parameters		
Age at which the first manifestation of the disease is noted	Under 2 years old	Older than 2 years
Splenomegaly	Moderate	Moderate to pronounced
Dependence on transfusions	Dependent	Non-dependent
Jaundice	–	+
Bone deformities	–	+
Hematological parameters		
Hb, g/dl	<6–7	≥6–7
HbF, %	>50	10–50
HbA2, %	<3,5	≥3,5
MCV	Normal	Decreased
Nucleated red blood cells	Normal	Increased
Leukocytes	Normal	Increased
Genetic parameters		
Parents	Both parents are heterozygotes for β-thalassemia	One or both parents atypical carriers of β-thalassemia
Types of mutation	Severe	From silent to mild
Co-inheritance	–	+
α-thalassemia	–	+
δβ-thalassemia	–	+
HPFH Gy XMN1 polymorphism	–	+

Note: Hb — hemoglobin; HbF — fetal hemoglobin; MCV — mean erythrocyte volume; NPFH — hereditary persistence of fetal hemoglobin.

Untreated NTDT causes various complications. The pathogenetic mechanisms of clinical complications are shown in Fig. 2.

Endocrine complications. Hypogonadism, hypothyroidism (HT), and diabetes mellitus (DM) occur in intermediate NTDT. In general, patients with NTDT are slightly delayed in their sexual development, although they remain fertile. Sometimes HT occurs in the older age group [13, 14].

Extramedullary erythropoiesis. Extramedullary erythropoiesis in intermediate thalassemia is a compensatory mechanism aimed at suppressing chronic anemia. It leads to the formation of erythroid tissue damaging the spleen, liver, lymph nodes, chest and spine [15]. These erythroid tissue masses can be detected by magnetic resonance imaging (MRI). Treatment follows an algorithm that includes blood transfusions, hydroxyurea therapy, laminectomy, and radiation therapy depending on the degree of neurological deterioration [16].

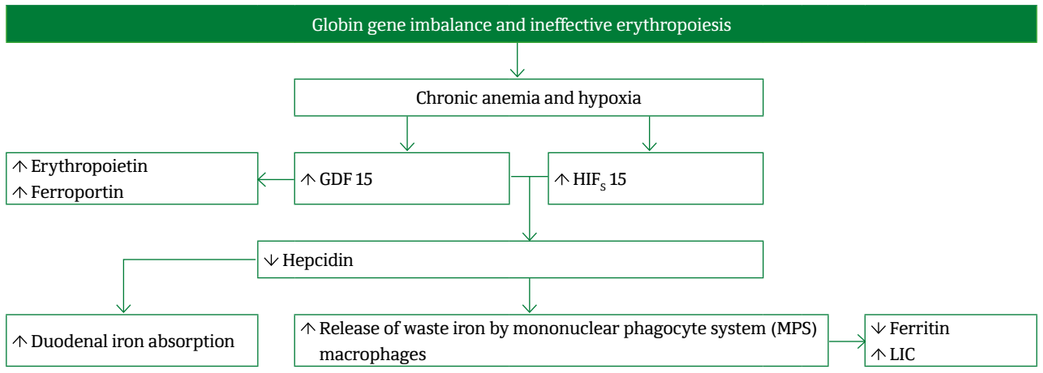


Fig. 1. Iron metabolism in patients with non-transfusion-dependent thalassemia [37]

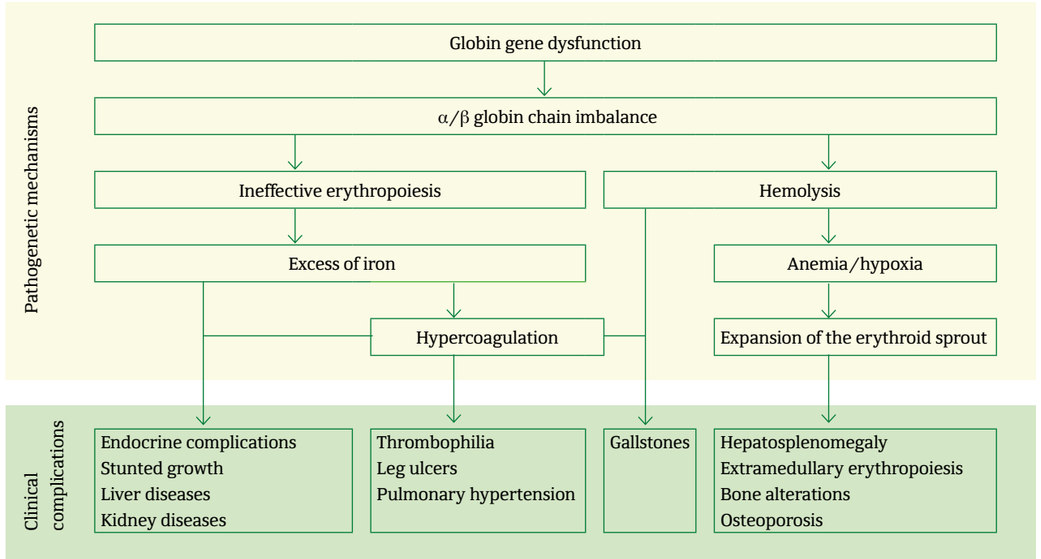


Fig. 2. Pathogenetic mechanisms and clinical complications of non-transfusion dependent thalassemia [5]

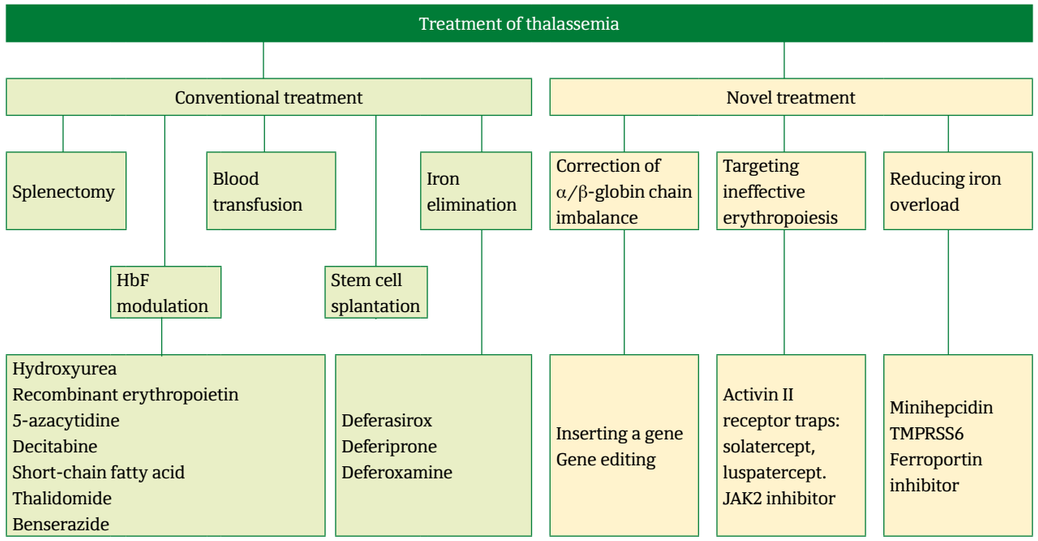


Fig. 3. Thalassemia treatment methods.

Note: HbF - fetal hemoglobin; JAK2 - janus kinase 2; TMPRSS6 - transmembrane protease serine 6; HIF2α - hypoxia-inducible factor 2α.

Liver Diseases. Due to the fact that in NTDT most of the iron accumulation occurs in the liver, patients are at increased risk of developing hepatic fibrosis, cirrhosis and eventually hepatocellular carcinoma (HCC), mainly in unchelated patients [17]. Iron overload is associated with the generation of toxic free radicals and also damages tumor suppressor genes and DNA repair genes. In addition, iron overload accelerates the process of liver cirrhosis due to its profibrogenic effect [18].

Gallstones in the gallbladder. Gallbladder stones are one of the most common complications of thalassemia. Stone formation is mainly related to iron deposition with subsequent hemolysis and ineffective erythropoiesis, which often leads to cholecystectomy [7, 19].

Kidney diseases. Iron overload is thought to play an important role in tubular and glomerular dysfunction. End-stage renal disease is a possible end result of anemia and renal damage mediated by iron overload. As a result of ineffective erythropoiesis and peripheral hemolysis, NTDT patients are prone to formation of renal stones, which in turn may lead to hydronephrosis and renal failure [20].

Trophic ulcers on the lower extremities. Most cases of ulcers occur in adult patients with NTDT. The pathogenesis of lower limb ulcers is the result of the interaction of many factors, especially chronic anemia and hypercoagulation. Ulcers are very painful and poorly amenable to therapy, but an intensive hemotransfusion regimen can alleviate the condition of patients. The addition of zinc preparations to therapy may promote ulcer healing. The administration of hydroxyurea and EPO, as well as their combination, can be helpful [21].

Thrombophilia. Hypercoagulable state in NTDT is associated with a high incidence of thromboembolic complications, such as deep vein thrombosis, portal vein thrombosis, pulmonary embolism, cerebral thrombosis, recurrent arterial thrombosis [22].

Pulmonary hypertension. The results of a multicenter study demonstrated a 5-fold increase in the incidence of pulmonary hypertension in NTDT compared with TDT [23]. While the etiology and mechanism of pulmonary hypertension are unclear, it has been reported that splenectomized patients with severe anemia and thrombosis are at higher risk [24].

Iron overload. Iron overload complications occur in both TDT and NTDT patients. However, in NTDT this is not due to hemotransfusions, but rather to increased absorption of iron in the intestine. As a result, iron overload leads to serious complications that include heart failure (HF) and endocrine disorders such as DM and hypogonadism. The prescription of chelation therapy depends on the amount of iron overload, iron accumulation, and the time of exposure to excess iron [25].

Bone anomalies/osteoporosis. Bone anomalies, including facial bone deformities, maxillary protrusion, maxillary sinus obliteration, and osteoporosis resulting from increased ineffective erythropoiesis and subsequent bone marrow expansion, are more severe in NTDT compared with TDT. Patients with NTDT that underwent splenectomy are at higher risk of osteoporosis, iron overload and low HbF [26]. Osteoporosis rates are significantly lower in patients receiving iron chelation therapy or hydroxyurea therapy [15]. The most recent Thalassemia International Federation (TIF) guidelines recommend that all patients over 10 years of age should be screened with annual bone mineral density assessment of the lumbar spine, femoral neck, and distal ulna using dual-energy X-ray absorptiometry [16].

Treatment of NTDT. Thalassemia treatment methods can be classified into conventional and novel ones [16, 27]. Conventional methods include splenectomy, transfusion therapy, modulation of HbF synthesis and bone marrow transplantation. Novel methods of thalassemia treatment can be divided into 3 groups according to the direction of influence on various elements of pathophysiology of the disease: imbalance of α/β-chains; hemolysis and ineffective erythropoiesis; excess of iron (Fig. 3).

Transfusion therapy. Although transfusion therapy is not currently the most common therapeutic option, it has a positive effect on NTDT patients. The decision to administer transfusion therapy should be based on the level of anemia, the presence of such symptoms as stunted growth and development, and their severity. The degree of iron overload varies in NTDT; therefore, an assessment of iron metabolism is recommended prior to transfusion therapy. To prevent transfusion dependence in NTDT patients, unlike in TDT patients with a regular hemotransfusion regimen, an individualized hemotransfusion regimen is recommended for this group of patients. Alloimmunization in patients with intermediate thalassemia is mildly more common; however, this risk is reduced when transfusion therapy is administered before 12 months of age [28].

Thalassemia treatment methods can be classified into conventional and novel ones [16, 27]. Conventional methods include splenectomy, transfusion therapy, modulation of HbF synthesis and bone marrow transplantation. Novel methods of thalassemia treatment can be divided into 3 groups according to the direction of influence on various elements of pathophysiology of the disease: imbalance of α/β-chains; hemolysis and ineffective erythropoiesis; excess of iron

Indications for transfusion therapy in non-transfusion dependent thalassemia [29]:

- hemoglobin level less than 50 g/l;
- decreased hemoglobin level accompanied by intensive growth of the spleen (more than 3 cm per year);
- stunted growth;
- decreased tolerance to physical activity;
- disruption of secondary puberty;
- pronounced bone alterations;
- pregnancy;
- infections;
- other specific complications (eg: HF, pulmonary hypertension, thromboembolic disease, lower extremity ulcers, priapism).

Chelation therapy. Iron overload in NTDT patients, in contrast to TDT patients, does not cause problems, especially if there is no need for regular hemotransfusions. Studies that have been done with MRI have shown that in NTDT, iron accumulates mainly in the liver and there is no tendency towards accumulation in the heart. Currently, 3 iron chelators are used [27]:

- deferoxamine: subcutaneously, at a dose of 40 mg/kg, for 8-12 h using specific pumps;
- deferiprone: orally, at a dose of 75-100 mg/kg, in 3 doses, 1 h before meals;
- deferasirox: orally, at a dose of 10-30 mg/kg, once in the morning.

All 3 drugs are fairly effective, and the choice of a drug for each patient is based on the level of iron overload, depends on the location of iron accumulation in the body, convenience of administration, side effects and cost of the drug.

Modulation of fetal hemoglobin. It is known that a high HbF level in NTDT is prognostically favorable. Increased γ-chain synthesis in HbF compensates for decreased β-chain synthesis, thus reducing the severity of ineffective erythropoiesis.

Consequently, an increase in HbF production leads to a decrease in anemia and, therefore, improves the well-being of NTDT patients. Two drugs are mainly used to modulate HbF levels: hydroxyurea and recombinant erythropoietin (rEPO).

Hydroxyurea has shown promise in improving Hb levels and reducing disease-related complications in patients with NTDT [30]. Numerous studies, including two meta-analyses involving 709 patients and 344 patients with NTDT, have shown a significant reduction in the need for blood transfusions after hydroxyurea treatment [31, 32]. The rates of complete response, with patients no longer requiring transfusions, were 42% and 53%, respectively, in the 2 studies, whereas the rates of partial response were 79% in both studies.

There are very few studies on the efficacy of rEPO in NTDT — only 3, and they were conducted on a small number of patients — from 3 to 10, which showed the following results: in one study there was no Hb elevation in any of the patients, in the other two — Hb elevation in 67 and 80% of patients, respectively [5].

Considering that we have the most experience in the application of rEPO in patients with intermediate thalassemia, it would be appropriate to present the results of our own studies in more detail.

We examined 58 patients with intermediate thalassemia. The preparation was administered in a dose of 10000 IU 3 times a week for 6 months. As a result of the investigations, an increase in Hb content was revealed in all patients, though to a different degree: in 39 (67.3%) — by more than 20.0 g/l, in 16 (27.5%) — by 10-20 g/l, in 3 (5.2%) — by less than 10 g/l [5, 33].

Bone marrow transplantation. Bone marrow transplantation is a proven method for the radical treatment of β-thalassemia, which is used worldwide with good results. If transplantation is performed before the age of 14 years, the overall survival rate is 90-96%, and the event-free survival rate is 83-93% [34]. The decision on the appropriateness of bone marrow transplantation is related to the subsequent quality of life and its expected duration, which is particularly relevant to patients with NTDT, especially in relatively mild disease severity. Bone marrow transplantation is not recommended in such patients.

The use of conventional therapies for patients with NTDT has led not only to an increase in life expectancy, but also to an improvement in quality of life [35]. However, due to the limitations and problems associated with the available conventional therapies, novel therapies are currently being developed.

Novel treatment for NTDT. In addition to already established therapies for TNT, new therapeutic approaches are being developed to treat this disease [36, 37].

New therapeutic approaches include Janus kinase 2 (JAK2) inhibition, hepcidin modulation, TMPRSS6 inhibition, apotransferrin, activin receptor-II trap ligands, hypoxia-inducible factor 2α (HIF2α) inhibition, and gene therapy. The mechanism of action of these approaches is different (Fig. 3).

Inhibition of JAK2. Janus kinase 2 is a cell signaling molecule that regulates erythropoiesis in response to EPO. Erythropoietin binds to its receptor (EPO-R) on the surface of erythroid cells when it enters the bloodstream. This interaction induces rapid phosphorylation of JAK2, which subsequently activates several targets for erythropoiesis as signal transducer and activator of transcription 5 (STAT5). Phosphorylated active JAK2 expression has been reported to be elevated in β-thalassemia [2, 38]. Active expression of JAK2 causes increased proliferation and decreased differentiation of erythroid progenitor cells, resulting in massive extramedullary erythropoiesis, hyperplasia, and hepatosplenomegaly.

Thus, inhibition of JAK2 expression is a potential approach to prevent ineffective erythropoiesis [39, 40]. The use of JAK2 inhibitors in mouse models has demonstrated the reversal of splenomegaly and improvement of ineffective erythropoiesis. A multicenter phase 2a study evaluating ruxolitinib (a JAK2 inhibitor) in patients with thalassemia showed a 26.8% reduction in spleen size, improved erythrocyte transfusion and a small improvement in pretransfusion Hb [41].

Hepcidin modulation. Iron overload in patients with β-thalassemia is known to develop due to relatively low hepcidin levels and increased duodenal iron absorption. Consequently, increasing hepcidin concentrations may prevent excessive iron absorption. When hepcidin agonists were used in mice, decreased iron levels in the liver and spleen, increased Hb levels, and decreased splenomegaly and extramedullary hematopoiesis in the liver were observed [42]. Unfortunately, attempts to synthesize a sufficient amount of hepcidin proved to be extremely difficult. An alternative approach is represented by the production of long-acting molecules called "minihepcidins". Minihepcidins are useful for reducing iron overload and splenomegaly and improve anemia by reducing ineffective erythropoiesis and increasing erythrocyte longevity [43].

Inhibition of TMPRSS6. The transmembrane protease serine 6 (TMPRSS6) plays an inhibitory role in hepcidin expression [44]. In mouse models with a deletion or decreased expression of TMPRSS6, increased hepcidin activity, lower levels of EPO, and increased total Hb were observed [45]. A highly specific and potent antisense oligonucleotide (ASO) targeting mouse and human TMPRSS6 mRNA was identified. Lowering TMPRSS6 levels with ASO treatment resulted in lower serum iron levels and transferrin saturation in animal models by a dose-dependent increase in hepcidin. A new ASO targeting TMPRSS6 was evaluated in a placebo-controlled, double-blind, randomized, single-center phase I clinical trial involving healthy volunteers [46]. The study showed that it effectively reduces plasma iron levels and has therapeutic potential for patients with β-thalassemia. These results prove that suppression of TMPRSS6 is a potential strategy to increase hepcidin expression and reduce iron overload.

NTDT exhibits inherent genetic heterogeneity, which is manifested by a wide genetic polymorphism. There are complex pathogenetic mechanisms underlying the disease, determining the clinical picture and leading to numerous complications. All this must be taken into account when developing a treatment strategy for NTDT. As a result of conventional methods of NTDT treatment, great success has been achieved, the duration and quality of life of patients have increased, and the possibility of their radical cure has appeared

Apotransferrin. Transferrin is the main carrier of iron, so it can reduce iron overload by binding to excess iron. Mouse models of β-thalassemia treated with apotransferrin showed normalization of plasma iron concentration, increased Hb, decreased reticulocytosis, decreased EPO, reversed splenomegaly, improved extramedullary hematopoiesis and increased hepcidin expression [47]. These results suggest that apotransferrin is useful for preventing iron overload, as well as for improving ineffective erythropoiesis.

Inhibition of HIF2α. Hypoxia-inducible factor 2α plays a regulatory role in FPN, hepcidin, and iron absorption in the duodenum, so it is a potential strategy to control iron metabolism in thalassemic patients. Studies in thalassemic mice with iron overload revealed low iron accumulation in the liver without worsening anemia after disruption of HIF2α signaling in the intestine [48]. It has been reported that the expression of divalent metal transporter 1 (DMT1), duodenal cytochrome B (DcytB) apical iron reductase and FPN is increased in the duodenum of Hbbth3/+ mice due to hypoxia and HIF2α stabilization and activity. In addition, Hbbth3/+ mice show improved tissue iron levels and anemia after genetic ablation of intestinal HIF2α [48]. This observation suggests that duodenal HIF2α may be a novel therapeutic approach in β-thalassemia to improve anemia and iron overload.

Activin receptor-II trap ligands. One potential approach to the treatment of β-thalassemia is ACE-011 and ACE-536 ligands-traps of activin-II receptor. They improve erythrocyte production and terminal erythrocyte differentiation in β-thalassemia in mice [49]. Dussiot M. et al. reported that RAP-011, an activin-IIA receptor ligand (ActRIIA) trap improves inefficient erythropoiesis, normalizes anemia and inhibits iron overload in a mouse model of intermediate β-thalassemia. Activin receptor ligand traps are the first approved pharmacological treatment for NTDT [50].

FPN inhibitors. Numerous therapeutic approaches that stimulate hepcidin activity have been studied and have shown promising results [37, 43]. A similar effect can be achieved with agents that directly inhibit FPN activity [37, 51]. The recently described oral FPN inhibitor VIT-2763 is known to block iron efflux, compete with hepcidin for binding to FPN, and induce FPN internalization and ubiquitination [52].

Conclusion. Thus, NTDT exhibits inherent genetic heterogeneity, which is manifested by a wide genetic polymorphism. There are complex pathogenetic mechanisms underlying the disease, determining the clinical picture and leading to numerous complications. All this must be taken into account when developing a treatment strategy for NTDT. As a result of conventional methods of NTDT treatment, great success has been achieved, the duration and quality of life of patients have increased, and the possibility of their radical cure has appeared. However, due to the limitations and problems associated with the available traditional methods, novel therapies are currently being developed.

References

1. Rivella S. Iron metabolism under conditions of ineffective erythropoiesis in β-thalassemia. *Blood*. 2019; 133(1):51–58. https://doi.org/10.1182/blood-2018-07-815928
2. Gupta R, Musallam KM, Taher AT, Rivella S. Ineffective Erythropoiesis: Anemia and Iron Overload. *Hematol Oncol Clin North Am*. 2018; 32(2):213–221. https://doi.org/10.1016/j.hoc.2017.11.009
3. Taher AT, Weatherall DJ, Cappellini MD. Thalassaemia. *Lancet*. 2018; 391(10116):155–67. http://dx.doi.org/10.1016/s0140-6736(17)31822-6

4. Taher AT, Musallam KM, Cappellini MD, Weatherall DJ. Optimal management of β thalassaemia intermedia. *Br J Haematol*. 2011; 152:512–523. https://doi.org/10.1111/j.1365-2141.2010.08486.x
5. Asadov C, Alimirzoeva Z, Mammadova T, Aliyeva G, Gafarova S, Mammadov J. β-Thalassemia Intermedia: A Comprehensive Overview and Novel Approaches. *Int J Hematol.* 2018; 108(1):5–21. https://doi.org/10.1007/2Fs12185-018-2411-9
6. Haidar R, Mhaidli H, Taher AT. Paraspinal extramedullary hematopoiesis in patients with thalassemia intermedia. *Eur Spine J*. 2010; 19(6):871–8. https://doi.org/10.1007/s00586-010-1357-2
7. Musallam KM, Cappellini MD, Wood JC, Taher AT. Iron overload in non-transfusion-dependent thalassemia: a clinical perspective. *Blood Rev*. 2012; 26 Suppl 1:S16–9. https://doi.org/10.1016/S0268-960X(12)70006-1
8. Porter JB, Cappellini MD, Kattamis A, Viprakasit V, Musallam KM, Zhu Z, et al. Iron overload across the spectrum of non-transfusion-dependent thalassaemias: role of erythropoiesis, splenectomy and transfusions. *Br J Haematol*. 2017; 176(2):288–299. https://doi.org/10.1111/bjh.14373
9. De Domenico I, Ward DM, Kaplan J. Hepcidin regulation: ironing out the details. *J Clin Investig*. 2007; 117(7):1755–8. https://doi.org/10.1172/jci32701
10. Peyssonnaux C, Zinkernagel AS, Schuepbach RA, Rankin E, Vaulont S, Haase VH, et al. Regulation of iron homeostasis by the hypoxia-inducible transcription factors (HIFs). *J Clin Investig*. 2007; 117(7):1926–32. https://doi.org/10.1172/JCI31370
11. Rivella S. The role of ineffective erythropoiesis in non-transfusion-dependent thalassemia. *Blood Rev.* 2012; 26 Suppl 1(01):S12–5. https://doi.org/10.1016/S0268-960X(12)70005-X
12. Tanno T, Bhanu NV, Oneal PA, Goh SH, Staker P, Lee YT, et al. High levels of GDF15 in thalassemia suppress expression of the iron regulatory protein hepcidin. *Nat Med.* 2007; 13(9):1096–101. https://doi.org/10.1038/nm1629
13. De Sanctis V, Soliman A, Elsedfy H, Skordis N, Kattamis C, Angastiniotis M, et al. Growth and endocrine disorders in thalassemia: The international network on endocrine complications in thalassemia (I-CET) position statement and guidelines. *Indian J Endocrinol Metab*. 2013; 17(1):8–18. https://doi.org/10.4103/2230-8210.107808
14. Casale M, Baldini MI, Del Monte P, Gigante A, Grandone A, Origa R, et al. Good Clinical Practice of the Italian Society of Thalassemia and Haemoglobinopathies (SITE) for the Management of Endocrine Complications in Patients with Haemoglobinopathies. *J Clin Med.* 2022; 11(7):1826. https://doi.org/ 10.3390/jcm11071826
15. Taher AT, Musallam KM, Karimi M, El-Beshlawy A, Belhoul K, Daar S, et al. Overview on practices in thalassemia intermedia management aiming for lowering complication rates across a region of endemicity: the OPTIMAL CARE study. *Blood.* 2010; 115(10):1886–92. https://doi.org/10.1182/blood-2009-09-243154
16. Taher A, Musallam K, Cappellini MD, editors. *Guidelines for the Management of Non Transfusion Dependent Thalassaemia (NTDT)*. 2nd ed. Nicosa (Cyprus): Thalassaemia International Federation; 2017.
17. Moukhadder HM, Halawi R, Cappellini MD, Taher AT. Hepatocellular carcinoma as an emerging morbidity in the thalassemia syndromes: A comprehensive review. *Cancer*. 2017; 123(5):751–758. https://doi.org/10.1002/cncr.30462
18. Kew MC. Hepatic iron overload and hepatocellular carcinoma. *Cancer Lett.* 2009; 286(1):38–43. https://doi.org/10.1016/j.canlet.2008.11.001
19. Khavari M, Hamidi A, Haghpanah S, Bagheri MH, Bardestani M, Hantooshzadeh R, et al. Frequency of Cholelithiasis in Patients With Beta-Thalassemia Intermedia With and Without Hydroxyurea. *Iran Red Crescent Med J*. 2014; 16(7):e18712. https://doi.org/10.5812/ircmj.18712
20. Mallat NS, Mallat SG, Musallam KM, Taher AT. Potential mechanisms for renal damage in beta-thalassemia. *J Nephrol*. 2013; 26(5):821–8. https://doi.org/10.5301/jn.5000253
21. Matta BN, Abbas O, Maakaron JE, Koussa S, Daderian RH, Taher AT. Leg ulcers in patients with β-thalassaemia intermedia: A single centre's experience. *J Eur Acad Dermatol Venereol*. 2014; 28(9):1245–1250. https://doi.org/10.1111/jdv.12211
22. Cappellini MD, Robbiolo L, Bottasso BM, Coppola R, Fiorelli G, Mannucci AP. Venous thromboembolism and hypercoagulability in splenectomized patients with thalassaemia intermedia. *Br J Haematol*. 2000; 111(2):467–73. https://doi.org/10.1046/j.1365-2141.2000.02376.x
23. Derchi G, Galanello R, Bina P, Cappellini MD, Piga A, Lai ME, et al. Prevalence and risk factors for pulmonary arterial hypertension in a large group of β-thalassemia patients using right heart catheterization: a Webthal study. *Circulation*. 2014; 129(3):338–45. https://doi.org/10.1161/CIRCULATIONAHA.113.002124
24. Karimi M, Musallam KM, Cappellini MD, Daar S, El-Beshlawy A, Belhoul K, et al. Risk factors for pulmonary hypertension in patients with β thalassemia intermedia. *Eur J Intern Med.* 2011; 22(6):607–10. https://doi.org/10.1016/j.ejim.2011.05.013
25. Bou–Fakhredin R, Bazarbachi A, Chaya B,Sleiman J, Cappellini MD, Taher AT. Iron overload and chelation therapy in non-transfusion dependent thalassemia. *Int J Mol Sci*. 2017; 18(12):2778. https://doi.org/10.3390/ijms18122778
26. Musallam KM, Taher AT, Cappellini MD, Sankaran VG. Clinical experience with fetal hemoglobin induction therapy in patients with β-thalassemia. *Blood.* 2013; 121:2199–2212. https://doi.org/10.1182%2Fblood-2012-10-408021
27. Cappellini MD, Farmakis D, Porter J, Taher A, editors. *Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT)*. 4th ed. Nicosia (Cyprus): Thalassaemia International Federation; 2021.
28. Asadov CD. Immunologic abnormalities in β-thalassemia. *J Blood Disord Transf.* 2014; 5(7):1000224. https://doi.org/10.4172/2155-9864.1000224
29. Taher A, Hershko C, Cappellini MD. Iron overload in thalassaemia intermedia: reassessment of iron chelation strategies. *Br J Haematol.* 2009; 147:634–640. https://doi.org/10.1111/j.1365-2141.2009.07848.x
30. Yasara N, Premawardhena A, Mettananda S. A comprehensive review of hydroxyurea for β-haemoglobinopathies: the role revisited during COVID-19 pandemic. *Orphanet J Rare Dis.* 2021; 16(1):114. https://doi.org/10.1186/s13023-021-01757-w
31. Lahoud OB, Willis V, Solomon WB. Phlebotomy and Hydroxyurea for Non-Transfusion Dependent Iron Overload in Beta-Thalassemia Intermedia. *Blood*. 2014; 124:4031–4031. https://doi.org/10.1182/blood.v124.21.4031.4031
32. Algiraigri AH, Wright NAM, Paolucci EO, Kassam A. Hydroxyurea for nontransfusion-dependent β-thalassemia: A systematic review and meta-analysis. *Hematol Oncol Stem Cell Ther.* 2017; 10:116–25. https://doi.org/10.1016/j.hemonc.2017.02.002
33. Asadov Ch, Alimirzoeva Z, Hasanova M, Mammadova T, Shirinova A. Clinical application of recombinant erythropoietin in beta-thalassemia intermedia. *Georgian Med News.* 2016; (255):86–92. PMID: 27441542
34. Baronciani D, Angelucci E, Potschger U, Gaziev J, Yesilipek A, Zecca M, et al. Hemopoietic stem cell transplantation in thalassemia: a report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry, 2000–2010. *Bone Marrow Transplant*. 2016; 51(4):536–41. https://doi.org/10.1038/bmt.2015.293
35. Vichinsky E. Non-transfusion-dependent thalassemia and thalassemia intermedia: epidemiology, complications, and management. *Curr Med Res Opin.* 2016; 32(1):191–204. https://doi.org/10.1185/03007995.2015.1110128
36. Cappellini MD, Motta I. New therapeutic targets in transfusion-dependent and -independent thalassemia. *Hematology Am Soc Hematol Educ Program*. 2017; 2017(1):278–283. https://doi.org/10.1182/asheducation-2017.1.278
37. Asadov Ch, Aliyeva G, Shirinova A, Alimirzoyrva Z. Rationale of ferroportin inhibition for β-thalassemia management. *Drugs of the Future*. 2022; 47(2):123–130. https://doi.org/10.1358/dof.2022.47.2.3335977
38. Melchiori L, Gardenghi S, Rivella S. β-Thalassemia: HiJAKing ineffective erythropoiesis and iron overload. *Adv Hematol*. 2010; 2010:938640. https://doi.org/10.1155/2010/938640
39. Melchiori L, Guy E, Libani I, Schiró R, Ramos P, Breda L, et al. Potential use of Jak2 inhibitors to limit ineffective erythropoiesis and reverse splenomegaly in β-thalassemia. *Blood*. 2008; 112(11):1877–1877. https://doi.org/10.1182/blood.V112.11.1877.1877
40. Libani IV, Guy EC, Melchiori L, Schiro R, Ramos P, Breda L, et al. Decreased differentiation of erythroid cells exacerbates ineffective erythropoiesis in β-thalassemia. *Blood*. 2008; 112(3):875–85. https://doi: 10.1182/blood-2007-12-126938
41. Taher AT, Karakas Z, Cassinerio E, Siritanaratkul N, Kattamis A, Maggio A, et al. Efficacy and safety of ruxolitinib in regularly transfused patients with thalassemia: results from a phase 2a study. *Blood*. 2018; 131(2):263–265. https://doi.org/10.1182/blood-2017-06-790121
42. Gardenghi S, Ramos P, Marongiu MF, Melchiori L, Breda L, Guy E, et al. Hepcidin as a therapeutic tool to limit iron overload and improve anemia in β-thalassemic mice. *J Clin Invest*. 2010; 120(12):4466–77. https://doi.org/10.1172/JCI41717
43. Casu C, Chessa R, Liu A, Gupta R, Drakesmith H, Fleming R, et al. Minihepcidins improve ineffective erythropoiesis and splenomegaly in a new mouse model of adult β-thalassemia major. *Haematologica*. 2020; 105(7):1835–1844. https://doi.org/10.3324/haematol.2018.212589
44. Finberg KE, Whittlesey RL, Fleming MD, Andrews NC. Down-regulation of Bmp/Smad signaling by Tmprss6 is required for maintenance of systemic iron homeostasis. *Blood*. 2010; 115(18):3817–26. https://doi.org/10.1182/blood-2009-05-224808
45. Nai A, Pagani A, Mandelli G, Lidonnici MR, Silvestri L, Ferrari G, et al. Deletion of TMPRSS6 attenuates the phenotype in a mouse model of β-thalassemia. *Blood*. 2012; 119(21):5021–9. https://doi.org/10.1182/blood-2012-01-401885
46. McCaleb M, Lickliter J, Dibble A, Schneider E, Aghajan M, Guo S, et al. Transmembrane protease, serine 6 (TMPRSS6) antisense oligonucleotide (IONIS-TMPRSS6-LRX) reduces plasma iron levels of healthy volunteers in a phase 1 clinical study. *Blood*. 2018; 132(Suppl_1):3634–3634. https://doi.org/10.1182/blood-2018-99-115339
47. Li H, Rybicki AC, Suzuka SM, von Bonsdorff L, Breuer W, Hall CB, et al. Transferrin therapy ameliorates disease in β-thalassemic mice. *Nat Med*. 2010; 16(2):177–82. https://doi.org/10.1038/nm.2073
48. Anderson ER, Taylor M, Xue X, Ramakrishnan SK, Martin A, Xie L, et al. Intestinal HIF2alpha promotes tissue-iron accumulation in disorders of iron overload with anemia. *Proc Natl Acad Sci USA*. 2013; 110(50):E4922–30. https://doi.org/10.1073/pnas.1314197110
49. Dussiot M, Maciel TT, Fricot A, Chartier C, Negre O, Veiga J, et al. An activin receptor IIA ligand trap corrects ineffective erythropoiesis in β-thalassemia. *Nat Med*. 2014; 20(4):398–407. https://doi.org/10.1038/nm.3468
50. Brancaleoni V, Nava I, Delbini P, Duca L, Motta I. Activin receptor-ligand trap for the treatment of β-thalassemia: a serendipitous discovery. *Mediterr J Hematol Infect Dis.* 2020; 12(1):e2020075. https://doi.org/10.4084/MJHID.2020.075
51. Motta I, Bou-Fakhredin R, Taher AT, Cappellini MD. Beta thalassemia: new therapeutic options beyond transfusion and iron chelation. *Drugs*. 2020; 80(11):1053–1063. https://doi.org/10.1007/s40265-020-01341-9
52. Porter J, Taher A, Viprakasit V, Kattamis A, Coates TD, Garbowski M, et al. Oral ferroportin inhibitor vamifeport for improving iron homeostasis and erythropoiesis in β-thalassemia: current evidence and future clinical development. *Expert Rev Hematol*. 2021; 14(7):633–644. https://doi.org/10.1080/17474086.2021.1935854

Information about the author:

Chingiz D. ogly Asadov — MD, PhD, Associate Professor, Senior Research Fellow, Haematology Department of National Center of Hematology and Transfusiology, Baku, Azerbaijan,
asadovchingiz@gmail.com, ORCID ID: 0000-0002-1707-372X

The authors declare no conflicts of interest.
The study was not sponsored.
Received 16.05.2022

Differential diagnosis of essential arterial hypertension and neurocirculatory asthenia of the hypertensive type

Datsko A.V.[2], Orlov F.A.[1,2,3], Petrova O.N.[2], Emanova I.A.[4]

[1] Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia
[2] FGKU «Main center of military medical expertise» of the Ministry of defense of the Russian Federation, Moscow, Russia
[3] FSBEI FPE RMACPE MON Russia, Moscow, Russia
[4] State Budgetary Healthcare Institution of the Moscow region Balashikha Regional Hospital, Balashikha, Russia

UDK 616-079.4
DOI: 10.53652/2782-1730-2022-3-2-60-77

Abstract. Neurocirculatory asthenia (NCA) of the hypertensive type (synonyms: vegetative-vascular dystonia of the hypertensive type, neurocirculatory dystonia (NCD) or hypertensive type of vegetative-vascular dysfunction) is one of the three main forms of NCA. This type includes vegetovascular disorders of the sympathetic part of the autonomic nervous system (ANS). First of all, it is characterized by an increase in systolic blood pressure (BP). Vegetative-vascular disorders syndrome with an inadequate BP response of blood pressure to any stimuli is typical for NCA. Hypertension is a chronic disease, the main manifestation of which is the syndrome of high blood pressure, which is not associated with the presence of pathological processes in which the increase in blood pressure is due to known causes (symptomatic arterial hypertension). When making an expert decision, it is necessary to use methods of non-invasive evaluation of the ANS state: the Kerdo index, the cold test, the ocular reflex (Dagnini–Aschner), the solar reflex (Toma–Ru), and the Vane–Solovyova tables.

Keywords: arterial hypertension, neurocirculatory asthenia, autonomic nervous system.

Introduction. Cardiovascular diseases (CVDs) are one of the most frequent causes of disability, dismissal and mortality among able-bodied population of our country [23]. The prevalence of CVDs reaches 16.8% in individuals from 18 to 45 years old. Prospective foreign studies demonstrate a stable tendency towards a decrease in the average age of patients with newly detected CVDs and towards a greater prevalence of this disease among young and middle-aged people [2, 4, 18, 22].

Hypertensive neurocirculatory asthenia (synonyms: hypertensive type vegetovascular dystonia, neurocirculatory dystonia (NCD), or hypertensive type of vegetovascular dysfunction) is one of the three main forms of NCA. According to Makolkin's classification proposed in 1986, this type includes vegetovascular disorders of the sympathetic department of the autonomic nervous system (ANS). Primarily, it is marked by its manifestation in the form of increase of systolic blood pressure (BP). NCA is characterized by a syndrome of vegeto-vascular disorders with inadequate response of BP to any stimuli [5].

Hypertensive disease, as defined by the Russian Society of Cardiology in 2010, is a chronic disease, the main manifestation of which is a syndrome of elevated BP, not associated with the presence of pathological processes in which the increase in BP is due to known causes (symptomatic arterial hypertension) [17, 27].

When making an expert decision, it has to be assumed that the diagnosis of hypertension is essentially clinical and anamnestic (at least 6 months of documented anamnesis).

Diagnosing hypertensive NCA is usually not so simple. For this purpose the parameters of daily BP monitoring, characteristics of systolic and diastolic BP in dynamics, as well as at physical load are studied. Clinical and instrumental investigations are performed: ultrasound, obligatory ECG, blood and urine tests. Neurocirculatory dystonia is often to be differentiated from hypertension, mainly with its early stages. The difficulty of diagnosis is determined by a great similarity of symptoms of NCD and the initial stages of hypertention, as well as due to the fact that both conditions mainly have a hyperdynamic type of circulation. Probably, anamnestic data and prospective observation are of maximal importance in differential diagnosis of NCD and Stage I hypertension. The most significant is the sign of unstable BP elevation in NCD and predominance of such elevation in clinical picture in patients with hypertension [14, 15].

According to a number of studies, even in stage I hypertension, there are often initial manifestations of pathological changes in vessels, without signs of lesions of "target organs" [17, 27]. [17, 27], while in NCA there are none. The distinctive differences in their course and body parameters allow to differentiate between NCA and hypertension and to make a correct diagnosis. In contrast to hypertension in NCA, transient or labile arterial hypertension (AH), diastolic BP (DBP) increase, ocular fundus vascular changes, proteinuria, clinical and instrumental signs of left ventricular (LV) hypertrophy are absent.

In contrast to hypertensive type NCA, hypertension is also characterized by:

- administration of sedatives does not affect the BP level;
- blood pressure rises regardless of the situation and time of day, it may rise at night and immediately after waking up;
- BP rarely stabilizes without hypotensive medication;
- Not only does the systolic blood pressure (SBP) rise, but also the DBP.

Material and methods. The present work is based on the results of a complex clinical-laboratory, hormonal and instrumental examination of 41 men aged 18-26 years, who were hospitalized and treated at the cardiology department of Cardiology Department of The Main Military Clinical Hospital named after N.N. Burdenko during the period of 2020-2021. Of these patients, 21 patients were diagnosed with stage I hypertension and 20 patients were diagnosed with hypertensive NCA.

When distributing the material, we followed Verification of the diagnosis and exclusion of symptomatic AH was performed on the basis of a two-stage examination system developed and recommended by the Institute of Clinical Cardiology named after A.L. Myasnikov of the Cardiology Research Center of the RAMS.

There were no additional inclusion criteria for patients in the study. However, persons older than 45 years, with clinical signs of ischemic heart disease (IHD), symptomatic arterial hypertension, other comorbidities of the cardiovascular system (CVS) and internal organs were not included in the study.

The patient examination program combined clinical signs and laboratory and instrumental methods, which made it possible to create a database for a computer later on. All obtained data were summarized in a formalized case history (CH), in which qualitative signs are presented in quantitative gradations, and quantitative parameters are given in their absolute values [6].

After clinical, laboratory, and instrumental examinations, the main parameters of which were included in the formalized CH, we applied mathematical methods for more detailed assessment of the ANS status [9, 10, 20, 28].

1. Calculation of the autonomic Kerdo index:

AI=(1-BPdiast. / HR)×100

Where: AI — autonomic index; BPdiast. — diastolic blood pressure value; HR — heart rate per minute.

Interpretation: in full autonomic equilibrium (eutonia) in the CVS AI=0. If the coefficient is positive, sympathetic influences prevail; if the numerical value of the coefficient is negative, parasympathetic tonus is increased.

2. Calculation of the Hildebrandt index:

Q=HR / BR

Where: HR — heart rate per minute; BR (breath rate) — is the number of breaths per minute.

Interpretation: a coefficient of 2.8-4.9 indicates normal intersystem correlations. Deviation from these values indicates the presence of disturbances in the activity of separate visceral systems. All the mentioned parameters can be investigated not only at rest but also under the loads in order to clarify the questions of the autonomic reactivity and the autonomic support of the activity. Depending on the identified value, the autonomic tone is evaluated as sympathetic, parasympathetic, mixed.

3. Cold pressor test.

Technique of the test: Blood pressure and heart rate are measured in the supine position. Then the subject puts the other hand up to the wrist into the water

at +4 °C and holds for 1 min, the BP and heart rate are recorded immediately after immersion, at 0.5 and 1 min after immersion, and then, after taking the hand out of the water, the BP and HR are recorded until they come to the initial level.

Evaluation of the test: normal autonomic reactivity — increase of systolic (upper) BP by 20 mm Hg, diastolic (lower) — by 10-20 mm Hg in 0.5-1 min. The maximum rise of BP is 30 s after the start of cooling. BP return to the initial level — in 2-3 min.

Pathological deviations:

- hyperexcitability of vasomotors (hyperreactivity) — strong elevation of SBP and DBP, meaning a pronounced sympathetic response (increased autonomic reactivity);
- decreased vasomotor excitability (hyporeactivity) — insignificant rise of BP (diastolic pressure rise less than 10 mm Hg), poor sympathetic reaction (decreased autonomic reactivity);
- decreased SBP and DBP — parasympathetic response (or perverse reactivity).

4. Hot water immersion test.

Immersion of the hand into hot water (44 °C) for 2-3 min.

Normally BP should fall. At a weak decrease an insufficient reactivity of the parasympathetic department is determined, at an increase — an excessively high reactivity of the sympathetic department.

5. The oculocardiac reflex (Dagnini Aschner).

Technique of the test: after lying at rest for 15 minutes the HR is counted for 1 minute (initial baseline). Then the fingertips are pressed on both eyeballs till a slight pain sensation appears. After 15-25 s, record the HR for 20 s. Normally the heart rate slows down by 6-12 beats per 1 min after a few seconds from the start of pressure.

Interpretation:

- normally decelerating HR — normal autonomic reactivity;
- strong deceleration (parasympathetic, vagal reaction) — increased autonomic reactivity;
- weak deceleration — decreased autonomic reactivity;
- no deceleration — perverse autonomic reactivity (sympathetic reactivity).

Due to the different initial HR (greater or less than 70-72 beats/min), the degree of change in HR can be calculated by the Galu formula. The heart rate deceleration according to the Galu formula is:

$$X=100\times HRT / HRB$$

Where: HRT — is the heart rate in the test; HRB — is the baseline heart rate; 100 — is the reference HR number. The normal X value for the oculocardiac reflex is -3.95±3.77.

6. Sino-carotid reflex (Cermak-Hering).

Technique of the test: after 15 minutes of adaptation (rest) in the supine position, HR is counted for 1 minute — baseline. Then with fingertips (index and thumb) press alternately (in 1.5-2 seconds) on the upper third of m. sternoclaidomastoideus, slightly below the angle of the lower jaw, until the pulsation of the carotid artery is felt. It is recommended to start the pressure on the right side, since the irritation effect on the right side is stronger than on the left. The pressure should be light, causing no pain, for 15-20 seconds. From the 15th second, start recording the heart rate for 10-15 seconds. Then the pressure is stopped and the HR is counted for 1 minute. You can also record the after-action condition at the 3rd and 5th minutes after the end of pressure. Sometimes BP, respiratory rate are recorded.

Interpretation: the values obtained in healthy subjects, are taken as normal HR change meaning normal autonomic reactivity. The degree of HR change can also be calculated using the Galu formula, with the normal X value for the sino-carotid reflex being 4.9±2.69. Values higher than this indicate increased autonomic reactivity, namely, increased parasympathetic or insufficient sympathetic activity; values lower than this indicate decreased autonomic reactivity. Increased HR indicates a perverse response. According to different authors, a slowdown of HR after 10 s by 12 beats/min, a decrease of BP by 10 mm Hg, a slowdown of breath rate are considered to be normal. Pathological deviations: sudden and significant slowing of HR without BP drop (vagocardial type); major BP drop (more than 10 mm Hg) without heart rate slowing (depressor type); dizziness, fainting without BP or pulse changes or with changes in these parameters (cerebral type) — BP rise.

7. Supraumbilical or epigastric reflex (Tom-Ru).

Technique of the test: at rest, in the supine position, with relaxed abdominal muscles, HR is measured. It is also possible to examine BP (baseline values). Apply pressure to the solar plexus by hand until pulsation of abdominal aorta is felt. At the 20-30th second from the start, HR is recorded for 20 s and converted to per minute.

Interpretation: the normal X value for the solar reflex is -2,75±2,74. The degree of severity (normal, elevated or pronounced, decreased and perverse reactivity) and the nature of the reaction (sympathetic, vagal or parasympathetic) are determined.

There are several types of reaction: 1) the reflex is absent or inverted (the pulse is insufficiently slowed or rapid) — sympathetic type of reaction; 2) the reflex is positive (slowing over 12 beats/min) — parasympathetic type; 3) slowing by 4-12 beats/min — normal type.

8. Vein-Solovyova table (Tab. 1).

The Vein-Solovyova table is probably the most complete available way to determine the ratio of sympathetic and parasympathetic ANS activity. It is also convenient that this ratio is considered in different systems of the organism. Each symptom in the table is evaluated according to a 5-point system. The number of examined

Table 1. Criteria underlying the study

Symptoms and indicators	Reaction		Score, points
	Sympathetic	Parasympathetic	
Eyes			
Sparkle	Increased	Normal, dim	2,4
Pupils	Dilated	Normal, narrowed	3,4
Palpebral fissure	Dilated	Normal, narrowed	1,9
Exophthalmos	Pronounced	Absent	2,4
Lacrimation	Normal	Increased	1,2
TOTAL	11,3		
Skin			
Colot	Pale	Tendency to redness	2,4
Vascular pattern	Not expressed	Increased, cyanosis of extremities, acrocyanosis	2,4
Greasiness	Normal	Normal	1,8
Dryness	Increased	Normal	1,8
Sweating	Reduced or increased viscous sweating	Increased secretion of liquid sweat	3,1
Dermographism	Pink, white	Intense red, towering	3,1
Body skin temperature	Decreased	Increased	2,9
Hand temperature	Cold	Warm	2,6
Subjective feelings	Numbness in extremities, paresthesias in extremities in the mornings	Hands and/or feet are sweaty, sudden hot flashes, redness	1,7
Pigmentation	Intensified	Decreased	1,5
TOTAL	23,3		
Thermoregulation			
Body temperature	Increased	Reduced	3,9
Chills-like hyperkinesis	Characteristic	Absent	4,1
Feeling of chills	Absent	Increased	2,9
Cold tolerance	Satisfactory	Poor	3,1
Heat tolerance	Intolerance to heat, stuffy rooms	Satisfactory, may have increased sensitivity to dry heated air	2,9
Fever in infections	Feverish course of infections	Relatively low	2,9
TOTAL	19,8		
Body weight			
Altered	Tendency to lose weight	Obesity, tendency to gain weight	3,2
Thirst			
Altered	Increased	Reduced	1,8

Table 1. Continue. Criteria underlying the study

Symptoms and indicators	Reaction		Score, points
	Sympathetic	Parasympathetic	
Appetite			
Altered	Elevated, but patients are lean	Reduced	1,9
Cardiovascular system			
Pulse	Tachycardia, labile tachycardia	Bradycardia, labile bradycardia, respiratory arrhythmia	4,1
Systolic BP	Elevated	Decreased or normal	4,9
Diastolic BP	Elevated	Decreased or normal	4,3
Subjective complaints	Heartbeat, feeling of pressure, "pounding," constricting pain in the heart area	A feeling of tightness in the heart area combined with arrhythmia, especially at night when lying down	2,6
Minute volume	Large	Small	4,4
Functions of the heart	Increased functions of automatism, conduction, contractility, excitability	Inhibition of automatism and conduction functions, reduction of excitability	3,6
ECG; HR	Sinus tachycardia, long recovery to baseline pulse after exercise	Sinus bradycardia, less than 60 beats/ min or arrhythmia	4,2
P wave	Increase	Decrease	3,0
P-Q interval	Interval value at the lower limit of normal	Interval lengthening by no more than 0.02 s (with flattening and small amplitude of the P wave)	3,4
S-T interval	Displacement below the isoline	Above isoline, rounding of ST segment	3,5
T wave	Flattened or biphasic	Increase in amplitude by 50%	3,8
QRS complex	Normal	Widening of the entire complex	3,1
TOTAL	44,9		
Vestibular manifestations			
Dizziness	Uncharacteristic	Frequently	3,0
Respiratory apparatus (respiratory system)			
Breath rate	Normal or increased frequency	Slow, deep	3,5
Breath volume per minute	Increased	Decreased	3,5
Blood filling of the lungs	Increased	Decreased	2,7
Bronchial lumen	Expanded	Narrowed	3,2
Bronchial muscles	Relaxed	Contracted	3,2
Subjective complaints		Feeling of pressure, tightness in the chest, attacks of suffocation with predominance of difficult breathing	2,3
TOTAL	15,2		

Table 1. Continue. Criteria underlying the study

Symptoms and indicators	Reaction		Score, points
	Sympathetic	Parasympathetic	
Gastrointestinal tract			
Salivation	Reduced	Increased	2,6
Saliva composition	Thick	Liquid	2,4
Acidity of gastric juice	Normal or decreased	Increased	3,1
Intestinal motility	Atonic constipation, weak peristalsis	Tendency to excessive gas formation, dyskinesia, spastic constipation, diarrhea	3,8
Nausea	Absent	Characteristic	3,2
Esophagus and stomach (X-ray)	Relaxation of esophageal muscles, weakening of tone and inhibition of peristalsis	Esophageal muscle contraction, increased gastric tone, and increased peristalsis	3,2
Small and large intestine (fluoroscopy)	Decreased tone and weakened peristalsis	Increased tone and peristalsis	3,4
Other subjective complaints	Absent	Heaviness in epigastrium, gripping pain in upper stomach, diarrhea or constipation	3,1
TOTAL	24,8		
Urination			
Altered	Polyuria, pale urine	Urge to urination, urine is concentrated	3,1
Alteration of water-salt metabolism			
Fluid retention	Absent	Tendency to edema	3,0
Adrenal glands			
Function	Increased secretion of catecholamines and corticosteroids	Inhibition of catecholamine and corticosteroid secretion	3,5
Thyroid gland			
Clinical condition	Function is intensified	Function is reduced	4,1
Basal metabolic rate, absorption	Increased	Decreased	4,0
TOTAL	8,1		
Pancreas			
Blood sugar level	Normal, elevated	Decreased	3,5
Sugar curve	Irritative, not returning to normal	Flat, torpid	3,7
Sexual disorders			
Subjective	Sometimes hyposexuality, but more often libido is elevated	Normal potency, sometimes premature ejaculation	2,1
Erection	Normal	Increased	2,1
Characterological, personality, emotional disorders			
Peculiarities	Passionate, temperamental, enthusiastic about work, irascible, overly sensitive to pain, volatile mood	Depressed, fearful, apathetic, emotionally "blunt", lack of impulses, a lot of neurasthenic, hypochondriacal complaints and manifestations	2,4

Table 1. Continue. Criteria underlying the study

Symptoms and indicators	Reaction		Score, points
	Sympathetic	Parasympathetic	
Workability			
Activity: — physical;	Increased	Reduced	2,5
— mental	Distracted, quickly distracted, unable to concentrate, rapid change of thoughts, higher activity in the evening	Ability to concentrate is good, attention is satisfactory but poverty of ideas, highest activity before lunch or prolonged but at a slower pace	2,0
Sleep			
Peculiarities	Late falling asleep and early waking up, sleep is short, restless, numerous dreams. Sleep disturbance, more often insomnia	Deep, prolonged sleep, delayed transition to active wakefulness in the morning. Increased sleepiness	2,7 3,0
Allergic reactions			
Clinical manifestations	Rare	Often	3,1
Lymphoid tissue			
Presence of changes	Never	Hypertrophied, especially in children (lymph glands, tonsils)	2,2
Blood			
Erythrocytes, number	Increased	Decreased	2,0
White blood cells	Tendency to shift towards myeloid elements	Tendency to shift towards lymphoid elements	2,3
Leukocytes, number	Increased	Decreased	2,3
Myelocytes	Normal	Increased	2,0
Lymphocytes	Normal	Increased	2,6
Eosinophils	Increased	Normal	2,8
ESR	Accelerated	Delayed	1,8
Coagulation	Accelerated	Delayed	2,2
Viscosity	Increased	Decreased	1,8
Acid-alkaline state	Acidosis. Decrease of alkaline reserve	Alkalosis. Increase in alkaline reserve	2,2
Cholesterol levels	Normal or reduced	Increased	1,6
Calcium	Increased	Decreased	2,5
Potassium	Decreased	Increased	2,6
K/Ca ratio	Increased	Decreased	2,2
Ketone bodies, level	Elevated	Decreased	1,2
Creatinine			1,2
Copper			1,2
Acetylcholine	Decreased	Increased	2,2
TOTAL	36,7		
Overall	**233,0**		

manifestations is calculated, namely, the sum of sympathetic and parasympathetic symptom scores. Then the probability of sympathetic (or parasympathetic) predominance is calculated for all the indicated symptoms and indicators of the table — general autonomic tone or in one of the functional systems, for example, cardiovascular or gastrointestinal system. If all symptoms were investigated, it is enough to estimate which sum of points (sympathetic or parasympathetic) prevails.

The following formulas are used to accurately estimate the predominance of sympathetic or parasympathetic ANS tonus according to the Vein-Solovyova table:

If $\frac{Nn}{233} < 0,5$ and $\frac{Nc}{233} < 0,5$, then

$$Pc = \frac{0,5-\frac{Nc}{233}}{1-\frac{Nc+Nn}{233}} x100\%; Pn = 100\% - Pc, \text{ or}$$

$$Pn = \frac{0,5-\frac{Nc}{233}}{1-\frac{Nc+Nn}{233}} x100\%; Pc = 100\% - Pn,$$

where: Nn — is the number of points indicating the presence of parasympathetic symptoms; Nc – is the number of points indicating the presence of sympathetic symptoms; 233 — is the sum of points of all symptoms or the sum of points of examined parameters of one of the functional systems; Pn — is the probability of parasympathetic manifestations predominance; Ps – sympathetic [1, 8].

At $\frac{N}{233} \geq 0,5$ Pc = 100%, Pn = 0%.

At $\frac{Nn}{233} \geq 0,5$ Pn = 100%, Pc = 0%.

9. Orthostatic test.

The orthostatic test (OT) is a simple and easily available method of assessing the state of the cardiovascular system and its autonomic regulation, which can be performed in ambulatory conditions during a short period of time. The orthostatic test allows assessing the adaptive capabilities and mechanisms of cardiovascular regulation [25]. Moreover, orthostatic exposure reflects the state of regulatory mechanisms, in particular the ANS, and partially humoral mechanisms [26]. At normal functioning of regulatory processes during OT, part of blood deposition in the lower trunk is compensated mainly by HR increase, whereas BP can change insignificantly. When one of the ANS departments dominates, various changes in BP occur. It is considered that BP reflects the state of sympathetic nervous system [19].

All subjects underwent an active 10-minute OP [21], in which the subject was first in the horizontal position for 10-15 min, accompanied by minute-by-minute measurement of BP and HR until two repeated values were obtained, which were taken as baseline values. Then the subject took an upright position, and BP and HR were recorded at the 5th and 10th minutes of orthostasis.

The response to OT was considered physiological (type 1) when BP increased by not more than 10 mm Hg, HR by 20 beats/min, and BP decreased by not more than 15 mm Hg at the 5th minute of orthostasis. In primary hypersympathicotonia (type 2) SBP and DBP increased by more than 10 mm Hg, and HR over 20 beats/min. Secondary hypersympathicotonia (type 3) was indicated by the decrease of SBP by more than 15 mm Hg with the excessive increase of DBP and HR.

The response to OT was considered physiological (type 1) when BP increased by not more than 10 mm Hg, HR by 20 beats/min, and BP decreased by not more than 15 mm Hg at the 5th minute of orthostasis. In primary hypersympathicotonia (type 2) SBP and DBP increased by more than 10 mm Hg, and HR over 20 beats/min. Secondary hypersympathicotonia (type 3) was indicated by the decrease of SBP by more than 15 mm Hg with the excessive increase of DBP and HR. In hyposympathicotonic type of response (type 4) to orthostasis HR remained almost unchanged in comparison with clinostasis position, which was accompanied by significant decreases of both SBP and DBP. The sympathicasthenic reaction type (type 5) was diagnosed when the physiological or hypersympathicotonic reaction at the 5th minute turned into hypersympathicotonic at the 10th minute [19, 25, 26].

Results were processed on a personal computer using Statistica 6.0 software. The Kolmogorov-Smirnov and Shapiro-Wilk criteria were used to check the distribution for normality. With normal distribution, quantitative characteristics were presented as mean ± standard deviation (M±a).

Relative values were compared using the ~~2~~-criterion. In all cases of hypothesis testing, differences were considered statistically significant at $p<0.05$ [3, 11, 12, 13].

Results and discussion. General characteristics of the examined patients with hypertension and NCA are presented in Table 2.

The table shows that the mean age of Stage I hypertensive patients was 29.4±11.9 years, in hypertensive NCA it was 21.9±9.5 years. NCA patients were younger, but the groups were comparable according to the main indicators. In both groups, age range of 18 to 30 years prevailed, and mean duration of AH in patients with hypertension was significantly longer than in patients with NCA and was 3.2±3.1 and 1.2±2.3 years, respectively. Hypertensive NCA was previously diagnosed in 9 patients with hypertension.

Table 2. Characteristics of the examined patients with neurocirculatory asthenia of hypertensive type and stage I hypertension

Indicators	Neurocirculatory asthenia of hypertensive type, n=20	Hypertension Stage I, n=21
Number of examined people	20	21
Age, years: 18-30; 30-45	16 (80) 4 (20)	12 (57,1) 9 (42,9)
Mean age	21,9±9,5	29,4±11,9
Mean duration of AH, years	1,2±2,3	3,2±3,1*
*p<0.05 when comparing patients with stage I hypertension and hypertensive NCA.		
Note. Hereinafter, the figures in the brackets are the percentage of patients.		

Table 3. The presence of risk factors for arterial hypertension in patients with neurocirculatory asthenia of the hypertensive type and hypertension

Risk factors	Neurocirculatory asthenia of the hypertensive type, n=20	Hypertension Stage I, n=21
Hereditary predisposition to AH	5 (25)	18 (85,7)*
Excess body weight	2 (10)	7 (33,3)
Smoking	6 (30)	12 (57,1)
Alcohol consumption	3 (15)	11 (52,3)
*p<0.05 when comparing patients with I stage hypertension and hypertensive NCA.		

The risk factors in the studied patients are presented in Table 3, where it is clear that excessive body weight, smoking, alcohol consumption (at least once a week in an amount over 150 ml) were more frequently observed in the patients with hypertension than in those with NCA. The hereditary factor for AH in the closest relatives was significantly more frequent in patients with hypertension compared to those with NCA — 87.5 and 25%, respectively.

A careful questioning of the patients allowed us to identify various subjective disorders of them. The most frequent clinical manifestations in both groups of patients were headaches (mostly unexplicit) — 85 and 95.2%, dizziness — 15 and 52.4%, neurotic disorders — from 100 to 61.9%, respectively. Headaches in patients with NCA were of diverse character, not always associated with an increase in BP, and more often had a migraine character. Their aggravation was associated with psycho-emotional tension and changes in meteorological conditions. Group 2 patients had headaches more often in the morning and evening hours, weakened by the middle of the day, were dull, pressing, localized mainly in the occipital area and were associated with destabilization of BP values. Dizziness was predominantly observed in Group 2 patients, was usually of a short-term nature and did not significantly affect the well-being.

Cardiac symptoms in NCA patients occurred in 35% of cases and were more diverse, ranging from a tingling sensation in the left side of the chest to a burning and squeezing sensation in the left side of the chest. In patients with hypertension, cardiac symptoms (28.57%) were usually associated with BP destabilization (23.8%) following a medication interruption or other conditions (stress, weather, physical or psychoemotional fatigue, etc.). They resolved or decreased as the BP decreased and the target level was reached.

There was no typical angina-like pattern of cardialgia characteristic of coronary disease in both groups of patients.

It is of interest that the examined individuals had recurrent heart palpitations, which were not always documented on electrocardiogram, and dyspnea on physical exertion. Moreover, these nonspecific complaints were more frequently noted in patients with hypertensive type NCA — 65 and 45%, respectively, compared to 52.3% and 28.6%.

Table 4. Clinical manifestations in the examined subjects

Clinical manifestations	Neurocirculatory asthenia of the hypertensive type, n=20	Hypertension Stage I, n=21
Headaches	17 (85)	20 (95,2)
Dizziness	3 (15)	11 (52,4)*
otic disorders (irritability, depression, unstable mood, etc.)	20 (100)	13 (61,9)*
Pain in the left side of the chest: – Associated with an increase in BP; – of nervous character	7 (35) 2 (10) 5 (85)	6 (28,57) 5 (23,8) 1 (4,76)
Occasional sensation of heart palpitations, heart beats	13 (65)	11 (52,3)
Dyspnea on physical exertion	9 (45)	6 (28,57)
Regularity of administration of hypotensive therapy: – episodically;	 5 (25) 1 (5)	 13 (61,9)* 8 (38,1)*
*p<0.05 when comparing patients with I stage hypertension and hypertensive NCA.		

Table 5. Four types of diurnal curves depending on the value of the diurnal index

The pattern of nocturnal BP decrease	Type	Percent of nocturnal BP decrease
Normal	Dipper	10–20
Insufficient	Non-dipper	0–10
Nocturnal hypertension	Night-peaker	менее 0
Excessive	Over-dipper	более 20

Table 6. Blood pressure parameters in the examined patients

Показатели	Neurocirculatory asthenia of the hypertensive type, n=20	Hypertension Stage I, n=21
Variation limits of SBP fluctuations, mm Hg.	120–180	125–180
Variation limits of DBP fluctuations, mm Hg.	70–90	70–95
Mean SBP, mm Hg.	151,2±12,2	156,5±2,2
Mean DBP, mm Hg.	79,0±12,6	78,0±13,1
Variation limits of mean hemodynamic BP, mm Hg.	60–90	69–109
Variation limits of mean hemodynamic BP, mm Hg.	87,0±98,0	118,0±15,6
Diurnal index of BP, mean	13%	9,8%*
*p<0.05 when comparing patients with I stage hypertension and hypertensive NCA.		

The regularity of administration of hypotensive therapy was regularly higher in patients with hypertension, from 38.1% to 61.9%.

Assessment of the peculiarities of daily BP rhythm is carried out on the basis of the results of daily BP monitoring. This examination is absolutely necessary for expert evaluation of a patient, decision-making on the prescription and appropriateness of the carried antihypertensive therapy correction. It is of great interest to assess the differences between the mean values of daytime and night-time BP, which is the expression of BP biphasic rhythm during a day. It is generally accepted, that a healthy person should have 10-20% decrease of SBP and DBP at night. The most simple and widely used in clinical practice method of assessing the diurnal rhythm of BP is the calculation of the degree of nocturnal BP decrease - Diurnal Index (DI) (Table 5).

Currently, it is considered to be proved that individuals with insufficient (less than 10%) decrease of BP during night hours and nocturnal hypertension have a greater risk of cardiovascular complications, which means that it is possible to talk about the established prognostic value of initial DI. The informative value of this index regarding the estimation of the effect of antihypertensive therapy is still debated.

Currently, it is considered to be proved that individuals with insufficient (less than 10%) decrease of BP during night hours and nocturnal hypertension have a greater risk of cardiovascular complications, which means that it is possible to talk about the established prognostic value of initial DI. The informative value of this index regarding the estimation of the effect of antihypertensive therapy is still debated

Patients with NCA showed SBP values within the range of 120 to 180 mm Hg, and in stage I hypertension patients - from 125 to 180 mm Hg, and DBP — from 70 to 90 and 70 to 95 mm Hg, respectively. Mean DI was 13% in NCA and 9.8% in hypertension.

The mean values of the main instrumental methods of cardiovascular examination in the examined patients are shown in Table 7.

Apart from 24-hour BP monitoring, all patients underwent electrocardiographic study, echocardiography, veloergometry, 24-hour Holter ECG monitoring. There were no significant differences in the mean values of main instrumental parameters, which gives relevance to the issues of differential diagnosis of these diseases. Only an increase of mean number of ventricular extrasystoles during a day in patients with hypertension was revealed, which did not exceed the reference value.

The presented materials allow to conclude that it is impossible to make a differential diagnosis of the two diseases using the main instrumental methods of investigation. For this purpose, mathematical assessment methods for the ANS state were included in the study (Table 8).

In patients with NCA the mean value of Kerdo index was positive and was +0.98±1.23, which indirectly indicates the prevalence of sympathetic influence in the examined subjects; in patients with hypertension the mean value of the index was obtained with "minus" sign (0.23±2.86), which reflects the increase of parasympathetic tone.

However, calculation of the Hildebrandt index for all participants of the study did not reveal the presence of abnormalities in the activity of individual visceral systems.

During coold pressor test the patients (11 patients (55%)) with hypertensive type of NCA prevailed with the marked sympathetic reaction (elevated vegetative reactivity). Among patients with hypertension 8 (38.1%) had weak sympathetic reaction (decreased autonomic reactivity)

During the Hot water immersion test the sympathetic type of response was revealed in 14 (70%) patients of the 1st group and in 10 (48%) patients of the 2nd group.

Evaluation of the oculocardiac reflex (Dagnini Aschner) revealed normal slowing of HR (normal vegetative reactivity) in 3 (15%) patients of the 1st group and in 5 (23,8%) — in the 2nd group; strong slowing down (parasympathetic, vagal reaction) — increased autonomic reactivity in 11 (55%) patients of the 1st group and in 6 (28,6%) patients of the 2nd group; weak deceleration — decreased autonomic reactivity in 4 (20%) patients of the 1st group and in 8 (38,1%) patients of the 2nd group; absence of HR slowing — perverse autonomic reactivity

Table 7. Mean values of the main instrumental methods of cardiovascular system examination in the examined patients

Parameters	Neurocirculatory asthenia of the hypertensive type, n=20	Hypertension Stage I, n=21
Electrocardiography		
ECG PQ, ms	0,14±0,01	0,14±0,01
ECG QRS, ms	0,09±0,01	0,09±0,01
ECG QT, ms	0,387±0,004	0,396±0,005
Echocardiography		
LV diastolic diameter, cm	5,03±0,11	5,51±0,07
LV systolic diameter, cm	3,51±0,105	3,7±0,08
LV diastolic volume, ml	127,38±5,3	131,03±4,31
LV systolic volume, ml	56,3±3,34	59,98±2,81
LV stroke volume, ml	65,1±5,14	66,7±2,66
LV cardiac output, ml	5,3±0,25	5,1±0,18
Ejection fraction, %	66,7±2,06	63,8±1,44
LV myocardial mass, g	138,2±3,03	142,3±5,18
IVS diastolic thickness, cm	0,85±0,032	0,9±0,032
IVS systolic thickness, cm	0,98±8,68	1,0±2,90
IVS systolic thickening, %	27,3±4,19	23,25±5,5
Diastolic thickness of LVPL, cm	0,89±0,02	0,9±0,04
LVPW systolic thickness, cm	1,3±0,55	1,7±0,16
LVPW systolic thickening, %	37,1±0,08	34,1±2,05
Left atrium size, cm	3,7±0,08	3,8±0,141
Systolic pressure in pulmonary artery, mm Hg	15,9±1,73	18,0±1,16
LV myocardial mass index	74,07±1,61	75,11±2,73
Veloergometry		
Power of the performed workload	133,8±7,61	129,05±15,31
SBP at peak workload	183,5±4,84	189,3±3,93
DBP at peak workload	100,71±1,62	101,9±1,42
HR at peak workload	131,4±5,04	143,6±2,04
24-hour Holter ECG monitoring		
Mean heart rate, beats/min	70,0±1,45	70,9±1,93
Number of SVEs, 24 hours	53,9±3,50	73,89±6,98
Number of VEs, 24 hours	43,14±1,085	159,86±34,9*

*p<0.05 when comparing patients with I stage hypertension and hypertensive NCA.

Table 8. Indicators of mathematical methods for assessment of the autonomic nervous system in the examined patients

Indices	Neurocirculatory asthenia of the hypertensive type, n=20	Hypertension Stage I, n=21
1. Kerdo index	+0,98±1,23	-0,23±2,86*
2. Hildebrandt Index	2,9±1,93	3,6±0,21
3. Cold pressor test:		
– normal autonomic activity;	3 (15)	5 (23,8)
– hyperreactivity (sympathetic response);	11 (55)	7*(33,3)
– hyporeactivity;	3 (15)	8*(38,1)
– parasympathetic response	3 (15)	1 (4,8)
4. Hot water immersion test:		
– sympathetic response;	14 (70)	10 (48)
– parasympathetic response	6 (30)	11 (52)
5. The oculocardiac reflex (Dagnini Aschner):		
– normal autonomic reactivity;	3 (15)	5 (23,8)
– increased autonomic reactivity;	11 (55)	6*(28,6)
– decreased autonomic reactivity;	4 (20)	8*(38,1)
– perverse autonomic reactivity (sympathetic reactivity)	1 (5)	2 (9,5)
6. Sino-carotid reflex (Cermak-Hering):		
– normal autonomic reactivity;	7 (35)	7 (33,3)
– increased autonomic reactivity;	9 (45)	8 (38)
– vagocardial type;	3 (15)	5 (23,8)
– depressor type	1 (5)	1 (4,9)
7. Supraumbilical or epigastric reflex (Tom-Ru):		
– the reflex is absent or inverted (sympathetic type);	13 (65)	7 (33,3)
– reflex is positive (parasympathetic type);	1 (5)	9* (42,9)
– pulse slowing by 4-12 bpm (normal type)	6 (30)	5 (23,8)
8. Vein-Solovyova table:		
– Pn, %;	78	22*
– Pc, %	34	66*
9. Orthostatic test:		
– physiological type of response to orthostasis;	7 (35)	8 (38,1)
– primary hypersympathicotonic;	5 (25)	7 (33,3)
– secondary hypersympathicotonic;	5 (25)	3 (14,3)
– sympathoasthenic	3 (15)	3 (14,3)

*p<0.05 when comparing patients with I stage hypertension and hypertensive NCA.

(sympathetic reactivity) in 1 (5%) patient of the 1st group and in 2 (9,5%) patients of the 2nd group.

Sino-carotid reflex (Cermak-Hering). The degree of change in HR calculated by the Galu formula (X) for the sinocarotid reflex is 4.9±2.69 in the normal range. Normal autonomic reactivity was detected in 7 (35%) patients in Group 1 and in 7 (33.3%) in Group 2. Values higher than 4.9±2.69 indicate increased autonomic reactivity and were detected in 9 (45%) and 8 (38%) patients, respectively. Significant slowing of HR without a drop in BP (vagocardial type) was detected in 3 (15%) patients of the 1st group and in 5 (23.8%) patients of the 2nd group. Decrease of BP over 10 mm Hg without pulse deceleration (depressor type) was detected in 1 patient in each group - 5 and 4.9%, respectively.

Supraumbilical or epigastric reflex (Tom-Ru): sympathetic type was detected in 13 (65%) patients in Group 1 and in 7 (33,3%) in Group 2; parasympathetic type — in 1 (5%) patient in Group 1 and in 9 (42,9%) patients in Group 2; normal type — in 6 (30%) patients in Group 1 and in 5 (23,8%) patients in Group 2.

Analysis of the Vein-Solovyova table showed an average probability of the prevalence of parasympathetic (Pn) manifestations in NCA patients — 78%, in hypertensive patients — 22%, and sympathetic (Ps) — 34 and 66%, respectively.

Physiological type of orthostatic response was observed in 7 (35%) patients of the 1st Group and in 8 (38,1%) patients of the 2nd Group; primary hypersympathicotonic — in 5 (25%) patients of the 1st Group and in 7 (33,3%) patients of the 2nd Group; secondary hypersympathicotonic — 5 (25%) patients of the 1st Group and 3 (14,3%) of the 2nd Group; sympathoasthenic — 3 (15%) of the 1st Group and 3 (14,3%) of the 2nd Group.

Thus, the use of the above-described techniques of the ANS state assessment will allow general practitioners to develop an objective approach to the diagnosis of its dysfunctions, as well as to make a differential diagnosis of hypertensive type NCA and Stage I hypertension.

Conclusions. To summarize, the following conclusions can be made:

- In both groups of patients comparable in age there were autonomic disturbances of varying severity, but in NCA patients there were more of them and their severity often prevailed in the clinical picture of the disease.
- There were no significant differences in the mean values of the main instrumental parameters between hypertensive NCA and stage I hypertensive patients.
- Mathematical evaluation of the history of laboratory and instrumental methods of examination significantly increases their diagnostic value and allows estimating the ANS condition of a patient for selective prescribing of treatment and estimating the probability of complications development.
- The most accurate methods of noninvasive evaluation of the ANS state in our study were Kerdo index, cold pressor test, oculocardiac reflex (Dagnini Aschner), upraumbilical or epigastric reflex (Tom-Ru), and Vein-Solovyova tables. Significant differences between the groups were obtained in these investigations.

References

1. Veyn AM, Voznesenskaya TG, Vorobyova OV. *Vegetativnye rasstroystva: Klinika, lecheniye, diagnostika*. A.M. Veyn, editor. Moscow: Meditsinskoe informatsionnoye agentstvo; 2003. 752 p. (In Russ.).
2. Avtandilov AG. *Arterial'naya gipertenziya u podrostkov muzhskogo pola*. Moscow: Russian Medical Academy of Continuous Professional Education; 1997. 285 p. (In Russ.).
3. Adler YuP, Markova EV, Granovsky YuV. *Planirovaniye eksperimenta pri poiske optimal'nykh usloviy*. Moscow: Nauka; 1971. (In Russ.).
4. Almazov VA, Shlyakhto EV, Sokolova L.A. *Pogranichnaya arterial'naya gipertenziya*. Saint-Petersburg: Hippocrates; 1992. 192 p. (In Russ.).
5. Anshelevich YuV, Gurvich T.R. Autonomic regulation of the heart in the circulatory dystonia. *Clinical Medicine*. 1987; 65(5):61–64. (In Russ.).
6. Bailey NTJ. *The mathematical approach to biology and medicine* / Translated from English by Kovalenko EG. Moscow: Mir; 1970. 326 p. (In Russ.).
7. Bulavin VV, Chapluk AL, Kalmanov AS, Datsko AV, Denisova MP. The role of risk-factors in formation of arterial hypertension in teenagers, prospective conscripts and conscripts. *Russian Military Medical Journal*. 2015; 336(11):56–60. (In Russ.)]. https://doi.org/10.17816/RMMJ74041
8. Wayne AM, Solov'eva AD, Kolosova OA. *Distoniya*. Moscow: Meditsina; 1981. 318 p. (In Russ.).
9. Grinshtein AM, Popova NA. *Vegetativnye sindromy*. Moscow: Meditsina; 1971. 308 p. (In Russ.).
10. Drobotya NV. *Gemodinamicheskiye reaktsii na vneshniye vozdeystviya u zdorovykh lyudey i u bolnykh neyrotsirculyatornoy distoniey*. In: Eksperimentalnaya i klinicheskaya fiziologiyakrovoobrashcheniya. Cheboksary; 1993. p. 85–89. (In Russ.).
11. Kluzhev VM, Ardashev VN. Application of mathematical modeling methods in clinical practice. *Russian Military Medical Journal*. 1997; (5):41–44. (In Russ.).
12. Lasted LB. *Introduction to medical decision making*. Bykhovskiy ML, editor; translated from English by Bykhovskaya IM. Moscow: Mir; 1991. 282 p. (In Russ.).
13. Lisenkov AN. *Mathematicheskiye methody planirovaniya mnogofaktornykh medico-biologicheskikh eksperimentov*. Moscow: Meditsina; 1979. 343 p. (In Russ.).
14. Makolkin VI, Abakumov SA. *Neyrotsirculatornaya distoniya v therapevticheskoy praktike*. Moscow: Meditsina; 1985. 192 p. (In Russ.).
15. Pokalev GM. *Neyrotsirkulatornaya distoniya*. Nizhniy Novgorod: Publishing house of the NGMI; 1994. 300 p. (In Russ.).
16. Resolution of the Government of the Russian Federation No. 565 of July 4, 2013 "On Approval of the Regulations on Military Medical Expertise". (In Russ.).

17. Guidelines for the treatment of arterial hypertension of the European Society for Hypertension (ESH) and the European Society of Cardiology (ESC), November 2017.
18. Savitskiy NN. O nomenklature i klassifikatsii zabolevaniy serdechno-sosudistoy sistemy nevrogennoy prirody. *Clinical Medicine*. 1964; 42(3):20. (In Russ.).
19. Sklyannaya EV. The role of orthostatic test in prognosis of arterial hypertension development in young adults. *Clinician*. 2018; 12(2):16–21. (In Russ.). https://doi.org/10.17650/1818-8338-2018-12-2-16-21
20. Snezhitskiy VA. Methodicheskiye aspekty provedeniya ortostaticheskikh prob dlya otsenki sostoyaniya vegetativnoy nervnoy sistemy i funktsii sinusovogo uzla. *Journal of the Grodno State Medical University*. 2006; (1):3–6. (In Russ.).
21. Solovyova SV, Tsertsek TN, Bakieva EM, Trusevich NV, Solovyov VS. Active orthostatic responses in healthy persons and AH and COPD patients in the Surgut-city. *Tyumen State University Herald*. 2014; (6):132–40. (In Russ.).
22. Sorokina TA. *Neyrotsirkulatornaya distoniya*. Riga: Zinatne; 1979. 176 p. (In Russ.).
23. Chazova IE, Danilov NM, Litvin AYu. *Refracternaya arterialnaya hipertoniya: Monografiya*. Moscow: Atmosfera; 2014. 256 p. (In Russ.).
24. Shklovskii BL, Prokhorchik AA. Military-medical examination for cardiovascular diseases in the central military clinical hospital. *Russian Military Medical Journal*. 2018; 339(6):9–17. (In Russ.). https://doi.org/10.17816/RMMJ72945
25. Hynynen E, Konttinen N, Kinnunen U, Kyröläinen H, Rusko H. The incidence of stress symptoms and heart rate variability during sleep and orthostatic test. *Eur J Appl Physiol*. 2011; 111(5):733–41. https://doi.org/10.1007/s00421-010-1698-x
26. Lee H, Kim HA. Orthostatic hypertension: An underestimated cause of orthostatic intolerance. *Clin Neurophysiol*. 2016; 127(4):2102–7. https://doi.org/10.1016/j. clinph. 2015.12.017
27. Mancia D, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013; 31(7):1281–357. https://doi.org/10.1097/01.hjh.0000431740.32696.cc. PMID: 23817082
28. Tzivoni D, Stern Z, Keren A, Stern S. Electrocardiographic characteristics of neurocirculatory asthenia during everyday activities. *Br Heart J*. 1980; 44(4):426–32. https://doi.org/10.1136/hrt.44.4.426
29. Kryukov EV, Fursov AN, Potekhin NP, Chernov SA, Zaharova EG. Gipertonicheskij kriz — klinicheskaya traktovka termina. *Klinicheskaya medicina*. 2021; 99(2):146–149. (In Russ.). DOI: 10.30629/0023-2149-2021-99-2-146-149

Information about the authors:

Andrej V. Datsko — Colonel of Medical Service, Chief Military Medical Expert of the Defense Ministry, Chief of the «Main center of military medical expertise» of the Ministry of defense of the Russian Federation, Moscow, Russia.

Filipp A. Orlov — MD, ScD, Associate Professor, Honored Doctor of the Russian Federation, Head of Therapeutic (Advisory) Department of Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia — **responsible for contacts**, **esculap1@rambler.ru**, ORCID: 0000-0002-7081-9623

Ol'ga N. Petrova — Lieutenant Colonel of the Medical Service, Head of the Department of Examination of Military Personnel and Special Expertise in the «Main center of military medical expertise» of the Ministry of defense of the Russian Federation, Moscow, Russia.

Inessa A. Emanova — doctor of the department of functional diagnostics, State Budgetary Healthcare Institution of the Moscow region Balashikha Regional Hospital, Balashikha, Russia.

The authors declare no conflicts of interest.
The study was not sponsored.
Received 28.04.2022.

ISSN: 2782-1730 (PRINT) / ISSN: 2713-0711 (ONLINE) / DOI:10.53652/2782-1730-2022-3-2
MEDICAL BULLETIN OF THE MAIN MILITARY CLINICAL HOSPITAL NAMED AFTER N.N. BURDENKO.
Scientific and practical edition.
Circulation 1000 copies. Format: 60–90 1/8. Sertificate of registration of mass media PI number FS77-78674 on July 10, 2020. The Bulletin is published quarterly. Signed for printing 17.06.2022.
Founder: The Main Military Clinical Hospital named after N.N. Burdenko.
Editorial board: The Main Military Clinical Hospital named after N.N. Burdenko. Gospital sq. 3105229, Moscow, Russia. Phone: +7 499 263 5555, +4509, +4512,+4513; e-mail: gvkg.300@mail.ru
The journal's articles are included in the independent database of the complete list of scientific papers — the Russian Science Citation Index (RSCI). Free access policy.
Electronic versions of the published issues of the journal are available online: hospitalburdenko.com.
Target audience: doctors of various clinical disciplines, health care organizers, doctors of related specialties, residents, postgraduates.

Journal production "Medical Bulletin of the Main Military Clinical Hospital named after N.N. Burdenko": Publishing house "Opinion Leader". 125183, Moscow, Likhoborskie Bugry st., 6, # 30.
Tel.: +7 926 317 4445; e-mail: opinionleaderph@gmail.com
Director of the publishing house: Anna Gurchiani. Issuing editor: Svetlana Episeeva. Design & layout: Elena Mappyrova. Photographer: Natalia Vremyachkina. Translator: Petr Radaev.